HEPATOLOGY

PRACTICE GUIDANCE | HEPATOLOGY, VOL. 65, NO. 1, 2017

Portal Hypertensive Bleeding in Cirrhosis: Risk Stratification, Diagnosis, and Management: 2016 Practice Guidance by the American Association for the Study of Liver Diseases

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A. Purpose and Scope of the Guidance

This guidance provides a data-supported approach to risk stratification, diagnosis, and management of patients with cirrhosis and portal hypertension (PH). A guidance document is different from a guideline. Guidelines are developed by a multidisciplinary panel of experts who rate the quality (level) of the evidence and the strength of each recommendation using the Grading of Recommendations Assessment, Development, and Evaluation system. A guidance document is developed by a panel of experts in the topic, and guidance statements, not recommendations, are put forward to help clinicians understand and implement the most recent evidence.

This guidance focuses on PH, varices, and variceal hemorrhage (VH), and statements are based on the following: (1) review of the recent literature using PubMed, giving more weight to large, well-designed, prospective trials and well-performed meta-analyses; (2) several consensus conferences among experts; and (3) the authors' years of experience caring for patients with cirrhosis and varices. Management of ascites and encephalopathy is addressed in other documents.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ASGE, American Society for Gastrointestinal Endoscopy; AUROC, area under the receiver operating curve; BRTO, balloon occluded retrograde transvenous obliteration; cACLD, compensated advanced chronic liver disease; CC, compensated cirrhosis; CLD, chronic liver disease; CSPH, clinically significant portal hypertension; CT, computed tomography; CTP, Child-Turcotte-Pugh; EGD, esophagogastroduodenoscopy; EV, esophageal varices; EVL, endoscopic variceal ligation; GEV, gastroesophageal varices; GEV1/2, GEV type 1/2; GI, gastrointestinal; GV, gastric varices; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; HVPG, hepatic venous pressure gradient; IGV1/IGV2, isolated GV type 1/2; INR, international normalized ratio; ISMN, isosorbide mononitrate; kPa, kilopascals; LS, liver stiffness; MAP, mean arterial pressure; MELD, Model for End-Stage Liver Disease; MRE, magnetic resonance elastography; NASH, nonalcoholic steatohepatitis; NITs, noninvasive tests; NO, nitric oxide; NSBBs, nonselective beta-blockers; PH, portal hypertension; PP, portal pressure; PRBC, packed red blood cell; PVT, portal vein thrombosis; RCTs, randomized ,controlled trials; SBP, spontaneous bacterial peritonitis; SMT, somatostatin; SS, spleen stiffness; SVR, sustained virological response; SWE, shear wave elastography; TE, transient elastography; TIPS, transjugular intrahepatic portosystemic shunt; VH, variceal hemorrhage; VP, vasopressin.

Received October 20, 2016; accepted October 20, 2016.

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Financial support to develop this practice guidance was provided by the American Association for the Study of Liver Diseases.

The practice guidance was approved by AASLD on September 26, 2016.

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View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.28906

Potential conflict of interest: Dr. Bosch consults for Gilead, Conatus, Exalenz, Actelion, Chiasma, and Novo A/S. Dr. Garcia-Tsao consults for BioVie, Conatus, Galectin and Intercept.

When little or no data exist from well-designed, prospective trials, emphasis is given to results from large series and reports from recognized experts. In this case, clinical studies needed to clarify that management are specified in a section on future research.

Practice guidelines for the diagnosis and treatment of gastroesophageal VH were published in 2007, endorsed by the American Association for the Study of Liver Diseases (AASLD), American College of Gastroenterology, American Gastroenterological Association, and American Society of Gastrointestinal Endoscopy (ASGE).[1] Since then, a number of randomized, controlled trials (RCTs) have advanced our approach to managing VH. Additionally, four international consensus conferences were held since then, where experts in the field evaluated the changes in pathophysiology, diagnosis, and management of varices and VH. These include two AASLD/European Association for the Study of the Liver single-topic conferences in 2007 (many of the recommendations from this conference were incorporated into the aforementioned guidelines)[2] and in 2013, and two Baveno consensus conferences in 2010[3] and in 2015.[4] In this updated practice guidance, recommendations derived from these consensus conferences were also incorporated, particularly those from the latest Baveno conference that took place in Baveno, Italy, in April 2015.

Perhaps the most relevant change in these recommendations has been the recognition of the different stages of cirrhosis,[5] so that recommendations are now focused on risk stratification and individualizing care for PH.

Intended for use by health care providers, this guidance identifies preferred approaches to the diagnostic, therapeutic, and preventive aspects of care of patients with PH. As with other guidance documents, it is not intended to replace clinical judgment, but rather to provide general guidance applicable to the majority of patients. They are intended to be flexible, in contrast to formal treatment recommendations or standards of care, which are inflexible policies designed to be followed in every case. Clinical considerations may justify a course of action that differs from this guidance.

B. Risk Stratification

Cirrhosis is a chronic condition with a high mortality. It constitutes the fifth-leading cause of adult deaths and ranks eighth in economic cost among the major illnesses.[6]

Cirrhosis is a heterogeneous disease that cannot be studied or managed as a single entity and is classified in two main prognostic stages: compensated and decompensated cirrhosis.[5,7] This classification depends on the presence or absence of clinically evident decompensating events (specifically ascites, VH, and encephalopathy [HE]), with a median survival in the compensated stage that exceeds 12 years, whereas it is only 1.8 years in patients who develop decompensation.[8] The Child-Turcotte-Pugh (CTP) classification has been used to stratify patients with cirrhosis. Patients with cirrhosis belonging to the CTP-A class are compensated, whereas those in the CTP-B/C class are mostly decompensated.

PH is the initial and main consequence of cirrhosis and is responsible for the majority of its complications. In fact, it has been shown that portal pressure (PP), determined by the hepatic venous pressure gradient (HVPG), is better than liver biopsy in predicting development of complications of cirrhosis in patients with chronic liver disease (CLD) without cirrhosis on liver biopsy.[9] Therefore, a new entity denominated compensated advanced chronic liver disease (cACLD) has been proposed, emphasizing that PH may occur

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before a formal anatomical diagnosis of cirrhosis is established.[4] This entity would encompass patients with cirrhosis and those with advanced liver fibrosis with PH (HVPG > 5 mm Hg). For ease of understanding, in the rest of this guidance, the entity of cACLD will be referred to as compensated cirrhosis (CC), both terms being interchangeable and acceptable by consensus.[4]

The stage of CC is asymptomatic, and it is the longest stage. Pathophysiological mechanisms are evolving at this stage, and therefore several substages are being recognized. Based on PP, patients with CC can be divided into those with mild PH (HVPG > 5 but < 10 mm Hg) and those with clinically significant portal hypertension (CSPH), defined by an HVPG ≥10 mm Hg. CSPH is associated with an increased risk of developing varices,[10] overt clinical decompensation (ascites, VH, and HE),[11] postsurgical decompensation,[12] and hepatocellular carcinoma (HCC).[13] This substaging is not only prognostically important, but, as mentioned below, the mechanisms maintaining PH at these substages are different, and therefore their therapeutic approach will be different.

CSPH is present in approximately 50%-60% of patients with CC without gastroesophageal varices (GEV).[10] Patients with GEV have, by definition, CSPH, because patients with GEV have an HVPG of at least 10 mm Hg.[14,15] Prognosis is worse in patients with CC with GEV compared to those without GEV.[16,17] Therefore, among patients with CSPH, two substages are recognized based on the absence or presence of GEV. It is important to recognize that although PH and its direct consequences (varices) form the bases of staging in CC, liver insufficiency, even at this stage, plays an important role, given that serum albumin and the Model for End-Stage Liver Disease (MELD) score are also independent predictors of decompensation.[11]

VH constitutes a decompensating event, but its mortality differs whether it presents as an isolated complication of cirrhosis (20% 5-year mortality) or whether it presents in association with other complications (over 80% 5-year mortality).[8]

Whereas in the past, emphasis had been placed on managing the direct complications of PH, varices, and VH, it is now clear that these complications cannot be considered in an isolated manner. Rather, they should be considered in the context of advances in the staging of cirrhosis and in the context of other complications of cirrhosis that may occur concomitant or subsequent to development of varices and VH.[4]

Stages of PH in cirrhosis are depicted in Fig. 1, and goals of therapy at each stage are shown in Table 1.

Guidance statements

- **Cirrhosis should be described, analyzed, and managed in two distinct clinical stages, compensated and decompensated, defined by the presence or absence of overt clinical complications of cirrhosis (ascites, VH, and HE).**
- **Patients with compensated cirrhosis should be substaged into those with mild PH and those with CSPH, an entity that predicts the development of more-advanced stages.**
- **Patients with CSPH are substaged into those with and without GEV.**
- **Treatment of PH differs depending on the stage and substages of cirrhosis, because prognosis and mechanisms of disease (and therefore therapeutic targets) are different.**

C. Epidemiology and Associated Conditions

GEV are present in approximately 50% of patients with cirrhosis, but this depends on the clinical stage. In patients with CC, GEV are present in 30%-40%, whereas they can be present in up to 85% of patients with decompensated cirrhosis.[18,19] In patients with CC, varices develop at a rate of 7%-8% per year,[10] and progression from small to large varices occurs at a rate of 10%-12% per year, with decompensated cirrhosis being an independent predictor of progression.[20] VH occurs at a rate of around 10%-15% per year and depends on the severity of liver disease, size of varices, and presence of red wale marks (areas of thinning of the variceal wall).[21,22] Six-week mortality, which is now recognized as the primary endpoint to assess the impact of therapies for acute VH,[4] ranges between 15% and 25%.[23-25]

Other factors associated with poor outcomes in patients with VH are the presence of bacterial infections and an HVPG >20 mm Hg, which is mostly observed in patients belonging to the CTP-C class.[26,27] If untreated, recurrent VH occurs in 60% of patients, usually within 1-2 years of index hemorrhage.[28]

Obesity and alcohol use are associated conditions of prognostic relevance in patients with cirrhosis, independent of etiology. Obesity has been shown to predict

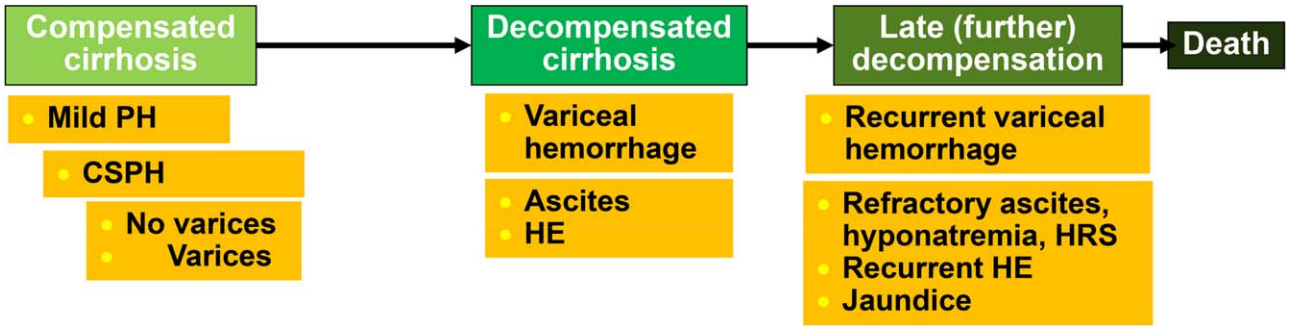

FIG. 1. Stages and substages of cirrhosis. The two main stages are the compensated and decompensated stages. The latter is characterized by the presence of clinically overt complications: ascites, VH, or HE. The compensated stage is the longest stage, and it is asymptomatic. There are at least two main substages of compensated cirrhosis with different prognostic and predominant pathophysiological mechanisms: patients with mild PH and those with CSPH. Patients in the latter stage are at risk of developing decompensation, particularly those who have GEV. The decompensated stage is much shorter and can rapidly progress to a stage of further decompensation in which renal failure (HRS) and liver failure (encephalopathy and jaundice) develop, leading to a high mortality.

worsening of liver fibrosis, cirrhosis decompensation, and lack of regression of cirrhosis in patients with viral cirrhosis,[29-31] whereas even moderate alcohol intake can lead to worsening PP and has been shown to worsen prognosis of hepatitis C virus (HCV)- and nonalcoholic steatohepatitis (NASH)-related cirrhosis.[32,33] Therefore, although beyond the scope of this guidance, weight loss and alcohol abstinence are important considerations in patients with cirrhosis.

D. Pathophysiological Bases of Therapy

PP increases initially as a consequence of an increased intrahepatic resistance to portal flow attributed to structural mechanisms (e.g., fibrous tissue, vascular distortion from regenerative nodules, and microthrombi; Fig. 2). This "structural" component, which explains around 70% of the increased intrahepatic resistance, could be targeted by treating the etiology of cirrhosis, the use of antifibrotic agents, and even anticoagulants.[34] However, at least one third of the increased intrahepatic resistance is attributed to an increased intrahepatic vascular tone, which, in turn, is attributed to endothelial dysfunction resulting mostly from reduced nitric oxide (NO) bioavailability.[35] This "functional" component is amenable to vasodilators (such as nitrates, alpha-adrenergic antagonists, and angiotensin-2 blockers).[36] These drugs should not be used alone, given that they also cause systemic vasodilatation, decrease arterial blood pressure, and may

TABLE 1. Stages of PH in Cirrhosis, Clinical Manifestations, and Goals of Therapy

Disease Stage	Compensated			Decompensated*		
HVPG	<10 mm Hg	≥10 mm Hg (CSPH)		≥12 mm Hg		
Varices	Absent	Absent	Present	Present		
Complications of PH	Absent	Absent	Absent	Acute VH	Previous VH without other complications†	Previous VH with other complications
Goals of therapy	Prevent CSPH	Prevent decompensation	Prevent decompensation (first bleeding episode)	Control bleeding, prevent early rebleeding and death	Prevent further decompensation (further bleeding) and other complications†	Prevent further decompensation and death/OLT

*Patients with decompensated cirrhosis (ascites, encephalopathy) without VH (past or present) are not considered in this table/review.
†Other complications = ascites, encephalopathy.
Abbreviation: OLT, orthotopic liver transplantation.

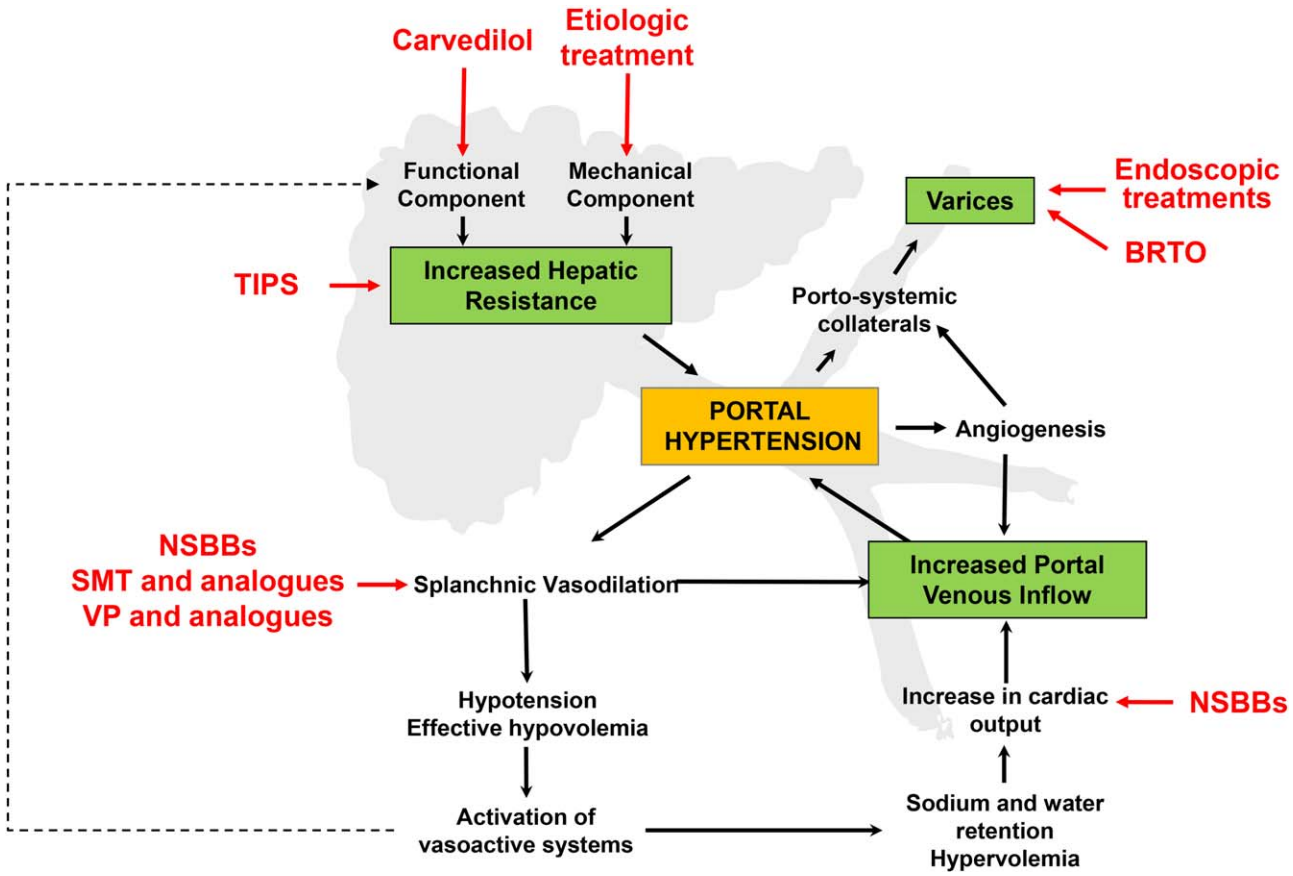

FIG. 2. Pathogenesis of PH and sites of action of *currently* recommended therapies to reduce PP or obliterate varices. In cirrhosis, PP increases initially as a consequence of an increased intrahepatic resistance to portal flow attributed to structural mechanisms (e.g., fibrous tissue, regenerative nodules) and an increased intrahepatic vascular tone (functional component). One of the initial consequences of PH is the formation of portosystemic collaterals. Concomitant or even preceding development of collaterals, splanchnic vasodilatation occurs, leading to increased flow into the gut and into the portal venous system. Vasodilation leads to activation of neurohumoral and vasoconstrictive systems, sodium and water retention, increased blood volume, and increased cardiac output; that is, a hyperdynamic circulatory state that further increases portal venous inflow and PP. Additionally, activated vasoconstrictive systems to further contribute to intrahepatic vasoconstriction. Treatment of etiology, by ameliorating fibrosis/inflammation, target the mechanical component of the increased intrahepatic resistance. Vasodilators (like the α-adrenergic blocking effect of carvedilol) target its functional component (this is the site of action of statins). NSBBs (β2-adrenergic blocking effect), SMT, and VP act by causing splanchnic vasoconstriction, thereby reducing portal venous inflow. NSBBs also act by decreasing cardiac output (β1-adrenergic blocking effect). The TIPS connects the hypertensive portal vein with a normotensive hepatic vein, thereby bypassing the site of increased resistance. Varices can be obliterated either endoscopically (EVL or cyanoacrylate injection) or by an endovascular approach (BRTO).

worsen sodium retention. A conceptually more appealing approach to ameliorate the functional component is to use drugs that will reduce PP by improving endothelial dysfunction, such as statins.[37] An added advantage of these drugs is that, by causing intrahepatic vasodilatation, they may improve hepatic blood flow and liver function. Statins in particular also have antifibrotic properties.[34]

One of the initial consequences of PH is the formation of portosystemic collaterals, the most important being those that develop through the coronary and/or short gastric veins and constitute GEV. Although formation of collaterals had been assumed to be the result of dilatation of preexisting vascular channels, research studies have implicated a process of neoangiogenesis.[38] Concomitant or even preceding the development of collaterals, splanchnic vasodilatation occurs, leading to increased flow into the gut and into the portal venous system. Therefore, even when portal flow is entirely diverted through collaterals, PH persists.[39] Increased splanchnic NO production is the main factor that leads to vasodilatation and increased splanchnic

blood flow. Hyperglucagonemia and neoangiogenesis further contribute to the increased splanchnic blood flow that maintains the portal hypertensive state.[38]

Vasodilation occurs not only in the splanchnic, but also in the systemic circulation (manifested clinically as arterial hypotension), leading to activation of neurohumoral and vasoconstrictive systems, sodium and water retention, increased blood volume, and increased cardiac output, that is, a hyperdynamic circulatory state that further increases portal venous inflow and PP. Additionally, norepinephrine, angiotensin-2, and antidiuretic hormone (activated neurohumoral and vasoconstrictive systems) further contribute to intrahepatic vasoconstriction.

Drugs that act by causing splanchnic vasoconstriction, such as non-selective beta-blockers (NSBBs; propranolol, nadolol, and carvedilol), vasopressin (VP), and its analogue, terlipressin, and somatostatin (SMT) and its analogues (octreotide, vapreotide) are known to reduce PP and constitute the current mainstay in the treatment of varices and VH. Given that these drugs act by decreasing flow to the splanchnic circulation and liver, an improvement in liver function would not be expected. β-1 adrenergic blockade decreases portal flow through a decrease in cardiac output, and β-2 blockade decreases portal flow through splanchnic vasoconstriction by unopposed α-adrenergic activity. Therefore, it is essential that beta-blockers used in the treatment of PH be nonselective. Importantly, the effect of NSBBs in decreasing flow is more related to their β-2 blocking effect rather than to their β-1 effect[40] and explains the lack of correlation between decreases in PP and decreases in heart rate.[41] Carvedilol, an NSBB with anti-α_1 adrenergic (vasodilator) activity, acts as an NSBB decreasing portal flow, but also acts as a vasodilator (intrahepatic circulation). HVPG response is greater with carvedilol than with propranolol or nadolol, but, given its vasodilatory properties, carvedilol is associated with a greater decrease in mean arterial pressure (MAP).[42]

It has been recently shown that patients with mild PH (HVPG $>$ 5 but $<$ 10 mm Hg) have a normal cardiac index (i.e., they have not yet developed the hyperdynamic circulatory state), whereas those with CSPH, especially if varices are present, have already developed a hyperdynamic state. Accordingly, response to NSBB in patients with mild PH is suboptimal compared to that of those with CSPH,[43] indicating that there is no role for NSBB in the setting of mild PH.

Endoscopic variceal ligation (EVL) is a local therapy that consists of placing rubber bands around esophageal varices (EV) in repeated sessions until they become obliterated. Because it is a local therapy that has no effect on PH, recurrence of varices is the rule, and patients require indefinite endoscopic monitoring.

Local therapies for management of gastric (mostly cardiofundal) varices consist of the (1) transendoscopic obturation by injection of cyanoacrylate glue into the varices or (2) transvenous obliteration by instillment of sclerosants and/or liquid embolic agents into a gastro-/splenorenal collateral through the left renal vein aided by balloon occlusion, that is, balloon occluded retrograde transvenous obliteration (BRTO).[44]

In patients with decompensated cirrhosis, placement of the transjugular intrahepatic portosystemic shunt (TIPS) by interventional radiological techniques that consist of connecting the hypertensive portal vein with a normotensive hepatic vein by a coated stent causes a significant decrease, and even normalization, of PP. Therefore, in patients with functional TIPS stents, there is no need for other therapies for PH (e.g., NSBB, EVL).

E. Diagnosis and Monitoring

PH is defined as a portal pressure gradient (the difference in pressure between the portal vein and the hepatic veins) greater than 5 mm Hg.

The best method to assess PP is through the catheterization of the hepatic vein with determination, through a balloon catheter, of the HVPG, which is the difference between the wedged (or occluded) hepatic venous pressure and the free hepatic venous pressure.[45] Normal HVPG is 3-5 mm Hg.

It should be underlined that the wedged (occluded) pressure (and, consequently, the HVPG) is a measure of sinusoidal pressure and does not provide useful data in prehepatic or presinusoidal PH (Table 2). An HVPG over 5 mm Hg identifies patients with cACLD/CC secondary to conditions associated with sinusoidal hypertension (Table 2). As mentioned above, PH is further defined as mild PH (HVPG $>$ 5 but $<$ 10 mm Hg) and as CSPH (HVPG $\geq$ 10 mm Hg). Above this threshold of 10 mm Hg, all the complications of PH are more likely to appear (varices, clinical decompensation).

In patients with GEV (who, by definition, have CSPH), an HVPG $>$ 12 mm Hg identifies bleeding

TABLE 2. Hepatic Vein Pressure Measurements in the Different Types of Portal Hypertension

		Hepatic Vein Pressure Measurement		
Type of PH*		Wedged (WHVP)	Free (FHVP)	Gradient† (HVPG)
Prehepatic (portal vein thrombosis)		Normal	Normal	Normal
Presinusoidal (cirrhosis attributed to cholestatic liver disease, schistosomiasis, and idiopathic portal hypertension)‡		Normal	Normal	Normal
Sinusoidal (cirrhosis attributed to alcohol/HCV/NASH)		↑	Normal	↑
Postsinusoidal	Sinusoidal obstruction syndrome	↑	Normal	↑
	Budd-Chiari syndrome	Unable to catheterize hepatic vein		
Posthepatic	Right heart failure	↑	↑	Normal

*PH is classified by the site of increased resistance to blood flow.
†Gradient or HVPG is calculated by subtracting the FHVP from the WHVP.
‡In advanced stages of presinusoidal causes of PH, the WHVP and HVPG will increase.
Abbreviations: WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; PH, portal hypertension.

risk, mostly because there is clear evidence that shows that reducing the HVPG to levels of 12 mm Hg or below is associated with protection from variceal hemorrhage (VH).[28] An HVPG > 16 mm Hg indicates a higher risk of death.[46] As mentioned previously, an HVPG ≥20 mm Hg predicts failure to control bleeding, early rebleeding, and death during acute VH,[27,47] and in patients with cirrhosis awaiting liver transplantation, each 1-mm-Hg increase in HVPG predicts a 3% increase in the risk of death in a median follow-up of 19 months.[48]

Despite the crucial role of HVPG in the determination of CSPH and other outcomes, HVPG measurements require specific expertise, are invasive, relatively expensive, and not available in all centers. Therefore, HVPG measurements are not considered standard of care for every patient with cirrhosis, particularly because noninvasive or surrogate indicators are increasingly utilized at most centers.

a) NONINVASIVE TESTS IN THE DIAGNOSIS OF CLINICALLY SIGNIFICANT PORTAL HYPERTENSION

In a step-wise diagnostic approach, specific signs of PH should be first looked for on physical examination. They include spider nevi or visible abdominal portosystemic collaterals. The absence of physical signs cannot be used to rule out CSPH.

Among laboratory data, a low platelet count is the most common laboratory sign of PH; it correlates slightly with HVPG and with the presence of GEV. However, taken alone, it is not accurate enough to either diagnose or exclude CSPH or GEV. On the other hand, the combination of platelet count with other unrelated noninvasive tests (NITs) improves the noninvasive diagnosis of CSPH.[49]

Ultrasound provides safe and inexpensive imaging evidence of morphological abnormalities associated with cirrhosis and PH. The presence of portocollateral circulation on ultrasound, computed tomography (CT), or magnetic resonance imaging (recanalized paraumbilical vein, spontaneous splenorenal circulation, and dilated left and short gastric veins) or the finding of a reversal of flow within the portal system is 100% specific for CSPH[50] and is sufficient to diagnose CSPH. Several other sonographic signs of PH have been described, such as dilatation of portal vein and the reduction of portal vein velocity (or their combination as congestion index of the portal vein).[51,52] Although splenomegaly taken alone is a sensitive, but nonspecific, sign of PH, the size of the spleen should be routinely reported, because, when combined with platelet count and liver stiffness, it provides accurate data on the presence of CSPH/varices.[49,53]

The ability to assess liver stiffness (LS), a physical property of liver tissue influenced by the amount of liver fibrosis content, has represented a major advance in this field. LS by transient elastography (TE; FibroScan) has proved very accurate for discriminating patients with and without CSPH, with a mean area under the receiver operating curve (AUROC) of 0.93 in a recent meta-analysis (based on five studies including 420 patients)[54] and can be currently considered the backbone of the noninvasive diagnosis of PH.

However, most of the data have been obtained in patients with untreated viral cirrhosis and alcoholic cirrhosis. Data regarding other etiologies and data in patients who have eliminated HCV require further investigation.

Most studies have shown that the best LS cutoff to detect CSPH is >20-25 kilopascals (kPa), with a diagnostic accuracy over 90%.[55,56] In a prospective study, HVPG ≥10 mm Hg and LS ≥21 kPa were equally effective in predicting decompensation.[57]

In a large study, an LSPS (liver stiffness [in kPa] × spleen size [in cm]/platelet count [in number/mm^3] score) > 2.06 was 90% specific in ruling in CSPH with a positive predictive value of >90%.[49] Importantly, these measures/scores have to be considered in the context of clinical parameters. In this sense, a recent prospective study described a sequential screening-diagnostic strategy based on LS measurements assessed in the context of the presence of any ultrasound abnormality and/or a platelet count <150,000/mm^3 and identified the subgroup of patients with CC in whom CSPH would be more likely.[56]

Spleen stiffness (SS) measurement by TE has been recently proposed as a novel parameter more tightly related to PH, with promising results.[58,59] In fact, SS > 54 kPa was better than LS and similar to HVPG in predicting first clinical decompensation in one study. However, SS cannot be measured by TE without a separate ultrasound exam and cannot be measured if the spleen is not significantly enlarged. Therefore, SS measurements by TE cannot be recommended in clinical practice.

Newer sonoelastographic methods allow direct visualization of the liver and spleen, facilitating SS measurement. Evidence is still limited, but point shear wave elastography (SWE; ARFI; Siemens, Germany)[60] and two-dimensional real-time SWE (Aixplorer; Supersonic Imagine, France)[61,62] show promising results with higher applicability and similar accuracy in the prediction of CSPH.

Magnetic resonance elastography (MRE) is an emerging technique that provides data on LS and SS of much larger areas of the liver and spleen compared to ultrasound-based techniques. Although MRE has been shown to be accurate in the staging of liver fibrosis,[63] data regarding its diagnostic performance in the diagnosis of CSPH are still very limited, with one study showing that LS determined by MRE predicted onset of clinical decompensation in patients with CC.[64] More studies are needed in this field.

Guidance statements

- **HVPG measurement is the gold-standard method to assess the presence of CSPH, defined as an HVPG ≥10 mm Hg.**
- **CSPH can be identified by noninvasive tests: LS > 20-25 kPa, alone or combined with platelet count and spleen size. The presence of portosystemic collaterals on imaging is sufficient to diagnose CSPH.**
- **Patients with GEV on endoscopy have, by definition, CSPH.**

b) NONINVASIVE TESTS IN THE DIAGNOSIS OF GASTROESOPHAGEAL VARICES

Determining the presence and size of varices and presence of red wale marks requires esophagogastroduodenoscopy (EGD), an invasive and expensive procedure that is not free of risks. Many studies have looked for noninvasive ways of determining the presence of high-risk varices (medium/large varices, i.e., those requiring prophylactic therapy) so as to circumvent the need for screening endoscopy.

The discriminative accuracy of NITs in predicting the presence of any GEV is limited (AUROC between 0.71 and 0.84),[55] and the use of NITs to diagnose GEV is not recommended. However, NITs are accurate to rule out high-risk varices in patients with CC. In particular, LS combined with platelet count correctly identifies patients at very low risk (<5%) of having high-risk varices.[56,65] These data have been obtained mostly from patients with untreated viral cirrhosis. Data in patients with NASH cirrhosis, cholestatic liver disease, and in those with HCV-related cirrhosis achieving sustained virological response (SVR) are needed.

By consensus among experts, and after review of the literature, it was proposed that patients with CC with LS <20 kPa (determined by TE) and a platelet count >150,000/mm^3 were very unlikely to have high-risk varices (<5%), and endoscopy could be safely avoided in them.[4] Unpublished studies have validated these cutoffs and report that 20%-25% of EGDs can be circumvented.

In patients with cirrhosis secondary to hepatitis B, an LSPS (liver stiffness [in kPa] × spleen size [in cm]/platelet count [in number/mm^3] score) < 3.5 was accurate in ruling out high-risk varices.[53] Whether this

cutoff can be applied to patients with cirrhosis attributed to other etiologies remains to be established.

Because measurements of SS are more feasible with ARFI, irrespective of spleen size, this technology is a promising tool in diagnosing and ruling out high-risk varices and compares favorably to other NITs in Asian studies[60]; however, data in European and American patients are lacking.

Guidance statements

- **Patients with an LS <20 kPa and platelet count >150,000/mm^3 have a very low probability (<5%) of having high-risk varices, and EGD can be circumvented**.
- **In patients who do not meet these criteria, screening endoscopy for the diagnosis of GEV is recommended when the diagnosis of cirrhosis is made**.

c) MONITORING THE DEVELOPMENT OF CLINICALLY SIGNIFICANT PORTAL HYPERTENSION, VARICES, AND HIGH-RISK VARICES

Patients without evidence of CSPH should be monitored to identify onset of the syndrome. Even if data on this specific aspect are lacking, data from published abstracts suggest that LS and platelet count monitoring could be useful. The appearance of new portosystemic collaterals during follow-up has been shown to be associated with variceal formation and growth,[66] as is progressive spleen enlargement.[67] Therefore, when performing screening for HCC, imaging evidence of worsening PH should be specifically sought.

Patients without varices on screening endoscopy constitute an area of uncertainty, given that their natural history has not yet been fully elucidated, particularly with the emergence of therapies that eliminate the etiologic agent.[68] Experts' opinion suggests that if liver injury is ongoing (e.g., active drinking in alcoholics and lack of SVR in HCV) and/or cofactors of disease are present (e.g., obesity, alcohol), surveillance endoscopy should be repeated at 2-year intervals. Otherwise, in the absence of ongoing injury, 3-year intervals are considered sufficient.[4] Although probably reasonable, there are no data to support discontinuing screening endoscopies if several of them are negative for varices.

In patients with small varices on screening endoscopy who are not candidates for primary prophylaxis (see below), repeat endoscopy is recommended. It has been suggested that if the liver injury is ongoing (e.g., active drinking in alcoholics and lack of SVR in HCV) and/or cofactors of disease are present (e.g., obesity), surveillance endoscopy should be repeated at yearly intervals. Otherwise, in the absence of ongoing injury, 2-year intervals are considered sufficient.[4]

Because development of decompensation could indicate worsening of PH and liver dysfunction with a higher incidence of cirrhosis, patients with no or small varices on screening endoscopy should have a repeat endoscopy performed when and if decompensation develops.

d) MONITORING CHANGES IN HEPATIC VENOUS PRESSURE GRADIENT

Changes in HVPG, spontaneous or during pharmacological therapy, have been shown to be predictive of outcomes. In patients with a history of VH, a decrease in HVPG to less than 12 mm Hg or a decrease greater than 20% from baseline significantly reduces the risk of recurrent hemorrhage, ascites, encephalopathy, and death.[69,70] In patients with CC, reductions in HVPG >10% from baseline have been associated with a reduction in development of varices,[10] first VH, and death.[71]

Recent studies show that the need for separate HVPG procedures to assess response to therapy can be obviated by assessing the acute hemodynamic response to intravenous propranolol (0.15 mg/kg) during a single procedure, but this requires further investigation.[71,72]

Unfortunately, there have been no NITs (e.g., Doppler, LS) that correlate with changes in HVPG.

Guidance statements

- **Patients with compensated cirrhosis (CC) without varices on screening endoscopy should have endoscopy repeated every 2 years (with ongoing liver injury or associated conditions, such as obesity and alcohol use) or every 3 years (if liver injury is quiescent, e.g., after viral elimination, alcohol abstinence)**.
- **Patients with CC with small varices on screening endoscopy should have endoscopy repeated every year (with ongoing liver injury) or every 2 years (if liver injury is quiescent, e.g., after viral elimination, alcohol abstinence)**.

- **Patients with CC without varices or with small varices who develop decompensation should have a repeat endoscopy when this occurs**.
- **Monitoring changes in HVPG should not be performed routinely (outside clinical trials). Noninvasive tests do not correlate well with changes in HVPG**.

F. Management

As mentioned above, therapy of varices and VH should be stratified according to the different clinical stages of cirrhosis and PH that are shown in Table 1. The objective of therapy for patients at an early stage is to prevent the development of later stages. Varices and VH should be managed in the context of the presence (or absence) of other complications of cirrhosis/PH (e.g., ascites, encephalopathy), and therefore the status (compensated or decompensated) of the patient with varices/VH should be always considered in the selection of the different therapies. In the compensated patient, the ultimate objective is to prevent decompensation; that is, the objective is not only to prevent varices or VH, but also to prevent the other complications of cirrhosis.

In addition to specific therapies that will be outlined below, in the compensated patient, every effort should be taken to eliminate the etiologic agent and to correct associated aggravating conditions, such as alcohol, obesity, and drug-induced liver injury, given that these measures, in themselves, can decrease portal pressure and reduce the risk of decompensation.

a) PATIENTS WITH COMPENSATED CIRRHOSIS AND MILD PORTAL HYPERTENSION

This stage is defined by an HVPG >5 but < 10 mm Hg. Patients in this stage do not have varices or other complications of PH and are known to have a very low risk of clinical decompensation in the following 5 years. Therefore, the goal of therapy is to prevent development of CSPH, which, clinically, would translate to prevention of GEV and clinical decompensation. Patients at this stage of cirrhosis have not yet reached the threshold of PP that predicts development of complications, and they have not yet fully developed a hyperdynamic circulatory state.[43] Therefore, because increased intrahepatic resistance is the main mechanism leading to PH in this stage, the mainstay of therapy has to be directed toward the etiology of cirrhosis. Livers of patients in this stage of cirrhosis are more likely to have thin fibrous septa compared to patients with CSPH.[73] Because thin septa are considered more susceptible to resorption/degradation, patients in this stage are the most likely to show regression to a noncirrhotic stage with treatment of etiology,[74] as has been demonstrated in patients with HBV (hepatitis B virus) cirrhosis.[31]

In addition to eliminating or suppressing the etiologic agent (e.g., HBV, HCV, alcohol, and iron), a number of drugs have been shown to have "antifibrotic" properties in preclinical studies, and some are currently being investigated in RCTs in patients mostly with compensated NASH cirrhosis (with and without CSPH).[75]

Statins decrease hepatic fibrogenesis, improve intrahepatic endothelial dysfunction, reduce PP, and improve liver perfusion and liver function.[76] In patients with compensated HCV cirrhosis, a propensity-score–matched study showed that statin users had lower incidence of decompensation (ascites and VH) and lower mortality than nonusers.[77] However, prospective, randomized trials of statins in patients with CC are lacking. Although statins appear to have a beneficial effect at all stages of cirrhosis,[76] the specific stage of cirrhosis that will be associated with maximal benefit from statins remains to be determined. This also applies to new antifibrotic agents.

Unfortunately, current NITs are not useful in ruling out CSPH. Therefore, the only way of confirming the absence of CSPH in patients without varices is by performing HVPG measurements. However, these measurements are not recommended in clinical practice, particularly given that treatment of etiology is the only currently recommended therapy in these patients, independent of substage. The specific identification of these patients by HVPG should be confined to clinical trials, in which the efficacy of targeted therapies and significance of reductions in HVPG to 5 mm Hg (or below) or magnitude of HVPG reductions from baseline should be explored.

Guidance statements

- **In patients in the earliest stage of compensated cirrhosis (patients with mild PH), the objective of treatment is to prevent development of CSPH/decompensation and perhaps even to achieve regression of cirrhosis**.
- **Elimination of the etiologic agent is the current mainstay of therapy**.

- **Drugs that act on portal flow, such as NSBBs, will be mostly ineffective in this substage, given that the hyperdynamic circulatory state is not fully developed**.

b) PATIENTS WITH COMPENSATED CIRRHOSIS AND CLINICALLY SIGNIFICANT PORTAL HYPERTENSION, BUT WITHOUT GASTROESOPHAGEAL VARICES

CSPH is defined as HVPG $\geq$10 mm Hg and is a hallmark in CC, given that it heralds the development of varices and clinical decompensation, among other outcomes. Livers of patients in this stage of cirrhosis mostly have thick fibrous septa and smaller nodules compared to those with mild PH.[73]

Until recently, it was considered that the aim of therapy at this stage of cirrhosis was to prevent development of GEV ("preprimary prophylaxis"). In this regard, a large, multicenter, randomized, placebo-controlled trial showed no differences between placebo and NSBB (timolol) in prevention of varices.[10] Therefore, no specific PP-reducing treatment to prevent formation of varices is recommended in this setting. Even though, at the time, it was considered that the study included a very homogeneous patient population (patients with cirrhosis without GEV), two distinct populations were identified: those with and without CSPH. The response to NSBB is different between groups; patients without CSPH (mild PH) have not yet developed a hyperdynamic circulatory state and therefore the reduction in PP observed in response to beta-blockers is significantly smaller in these patients than in those with CSPH.[43] Negative results of the timolol study are partly explainable because roughly half the patients did not have CSPH.

This study also showed that a decrease in HVPG >10% from baseline identified patients unlikely to develop varices.[10] More important, changes in HVPG in this setting could be surrogates of the development (or not) of clinical decompensating events. Whereas reduction or maintenance of HVPG to levels below 12 mm Hg likely prevents patients from developing VH and ascites, the percent reduction in HVPG from baseline associated with decreased risk of clinical outcomes remains to be determined.

It is now considered that the objective of therapy in patients at this stage is not only to prevent GEV, but, more important, to prevent decompensation. Drugs that will decrease intrahepatic resistance and/or decrease splanchnic blood flow are reasonable at this stage. Results of ongoing trials using NSBB and exploring this objective are eagerly awaited.

Guidance statements

- **In patients with cirrhosis and CSPH but without varices, the objective of treatment should no longer be to prevent varices, but to prevent clinical decompensation**.
- **There is no evidence at present to recommend the use of NSBBs in preventing formation of varices**.

c) PATIENTS WITH COMPENSATED CIRRHOSIS AND GASTROESOPHAGEAL VARICES

Patients at this stage have endoscopically proven GEV and have, by definition, CSPH, because the lowest HVPG in these patients is 10-12 mm Hg.[14,15] This clinical setting was previously described as "primary prophylaxis of variceal hemorrhage," and the main objective was to prevent the first episode of VH. In this setting, a reduction in HVPG to $\leq$12 mm Hg or $\geq$ 20% from baseline was shown to be protective of development of VH and constitutes an "optimal response" to NSBBs.[70] It is important to emphasize that changes in heart rate do not correlate with changes in HVPG, and that NITs are not useful in assessing changes in HVPG. Additionally, the beneficial effect of NSBBs may go beyond their PP-reducing effect, and therefore monitoring changes in HVPG should not be performed routinely.

As already mentioned, prevention of clinical decompensation is probably the most appropriate endpoint at this stage because ascites, not variceal bleeding, is the most common decompensating event,[11] and patients with varices, compared to those without varices, are more likely to decompensate.[16]

Therapies that would act on the pathophysiological mechanisms of PH/hyperdynamic circulatory state would theoretically prevent not only VH, but other complications of cirrhosis, whereas local therapies, such as EVL, which may prevent VH but would not prevent the other complications, would only play a role in patients intolerant to pathophysiologically targeted therapies.

In fact, reductions in HVPG >10% induced by use of NSBBs in the prevention of first hemorrhage are associated not only with a lower incidence of first VH,

but also to a lower incidence of ascites and death.[71,78] A decreased incidence of clinical decompensation has also been observed with reductions in HVPG >20% from baseline or to levels below 12 mm Hg.[79] However, these findings are not consistent.[80]

Other than these post-hoc analyses, there are no prospective studies specifically designed to assess therapies to prevent decompensation in patients with EV. Therefore, current recommendations are only pertinent with regards to prevention of first VH and are applicable to patients with both compensated and decompensated cirrhosis.

Primary prophylaxis of VH is indicated in patients at a high risk of bleeding. These are (1) patients with medium/large varices; (2) patients with small varices with red wale signs; and (3) decompensated patients with small varices.[81]

c.1. Prevention of First Variceal Hemorrhage in Patients With Medium/Large Esophageal Varices

The most recent meta-analyses of eight RCTs comparing NSBBs to no therapy/placebo[22] showed a benefit of NSBBs in preventing first VH. A meta-analysis of 19 RCTs (including unpublished abstracts) comparing NSBBs to EVL[82] showed that EVL was associated with lower rates of upper gastrointestinal (GI) bleeding and VH, without differences in mortality. The beneficial effect of EVL on bleeding was not confirmed in subgroup analyses limited to seven trials with adequate bias control or to 12 fully published studies.[82,83] Therefore, it has been recommended, by consensus, that either NSBBs (propranolol, nadolol) or EVL can be used to prevent first VH in patients with medium/large varices, and that choice of treatment should be based on local resources and expertise, patient preference and characteristics, contraindications and adverse events.[3,4]

Based on two trials comparing EVL to carvedilol that showed either a greater efficacy of carvedilol[84] or comparable efficacy,[85] carvedilol was added to the list of NSBBs that can be used in this setting (Table 3).[4]

Advantages of NSBBs include low cost, ease of administration, and not requiring specific expertise. In addition, and as mentioned previously, hemodynamic responders to NSBBs have a lower incidence of decompensation and death.

Importantly, because clinical trials proving the benefit of NSBBs did not routinely repeat EGD, and those that did showed no clear modification in variceal size; once a patient is on NSBBs, there is no need for repeat EGD.

Disadvantages of NSBBs are that approximately 15% of patients may have absolute or relative contraindications to therapy, and another 15% require dose reduction or discontinuation attributed to common side effects (e.g., fatigue, weakness, and shortness of breath) that resolve upon discontinuation, but that may discourage patients and their physicians from using these drugs.[86]

In cases in which NSBBs have to be discontinued because of intolerance, the patient can be switched to carvedilol, given that it is generally perceived as being better tolerated than traditional NSBBs. Dosing of carvedilol is also easier, given that it is not guided by heart rate and is at a start dose of 3.125 mg twice-daily and increased to a maximum dose of 6.25 mg twice-daily (Table 3). In patients intolerant to even the lowest dose of carvedilol, treatment should be switched to serial EVL.

Advantages of EVL are that it can theoretically be done in the same session as screening endoscopy and has few contraindications. Disadvantages are the risks associated with sedation, plus the risk of causing dysphagia, esophageal ulcerations, strictures, and bleeding. Although the number of side effects is greater with NSBBs, the severity of side effects is greater with EVL, with reports of deaths resulting from EVL-induced bleeding ulcers. In addition, because EVL is a local therapy that does not act on the pathophysiology of PH, not only is it unable to prevent complications other than VH, but also, after variceal eradication, surveillance endoscopies are necessary to detect variceal recurrence, which approaches 90%.

Subjective factors influence the physician's choice in selecting NSBBs versus EVL, as illustrated in a recent study in which gastroenterologists who spent at least half their time performing endoscopy were more likely to choose EVL, whereas physicians who had a less procedural-based practice were more likely to choose NSBBs.[87]

There is only one RCT comparing the combination of NSBBs plus EVL versus EVL alone in the prevention of first VH that showed no differences in the incidence of bleeding or death between groups, with an expectedly higher number of side effects in the combination therapy group.[88] Combination therapy is therefore not recommended in this setting.

Based on evidence obtained from trials of prophylactic surgical shunt therapy that show a significantly higher rate of encephalopathy and a tendency for a higher mortality in patients randomized to shunt surgery, TIPS (a shunt therapy) is not recommended in this setting.[89]

TABLE 3. Management of Patients With Moderate/Large Varices That Have Not Bled

Therapy	Recommended Dose	Therapy Goals	Maintenance/Follow-up
Propranolol	• 20-40 mg orally *twice* a day • Adjust every 2-3 days until treatment goal is achieved • Maximal daily dose: ○ 320 mg/day in patients without ascites ○ 160 mg/day in patients with ascites	• Resting heart rate of 55-60 beats per minute • Systolic blood pressure should not decrease <90 mm Hg	• At every outpatient visit make sure that heart rate is on target • Continue indefinitely • No need for follow-up EGD
Nadolol	• 20-40 mg orally *once* a day • Adjust every 2-3 days until treatment goal is achieved • Maximal daily dose: ○ 160 mg/day in patients without ascites ○ 80 mg/day in patients with ascites	• Resting heart rate of 55-60 beats per minute • Systolic blood pressure should not decrease <90 mm Hg	• At every outpatient visit make sure that heart rate is on target • Continue indefinitely • No need for follow-up EGD
Carvedilol	• Start with 6.25 mg *once* a day • After 3 days increase to 6.5 mg twice-daily • Maximal dose: 12.5 mg/day (except in patients with persistent arterial hypertension)	• Systolic arterial blood pressure should not decrease <90 mm Hg	• Continue indefinitely • No need for follow-up EGD
EVL	• Every 2-8 weeks until the eradication of varices	• Variceal eradication (no further ligation possible)	• First EGD performed 3-6 months after eradication and every 6-12 months thereafter

Any of these four therapies can be used, but current data do not support the use of combination therapy.

Guidance statements

- **Either traditional NSBBs (propranolol, nadolol), carvedilol, or EVL is recommended for the prevention of first VH (primary prophylaxis) in patients with medium or large varices (Table 3 for doses and schedules).**
- **Choice of treatment should be based on patient preference and characteristics.**
- **Patients on NSBBs or carvedilol for primary prophylaxis do not require monitoring with serial EGD.**
- **Combination therapy NSBB plus EVL is *not* recommended in this setting.**
- **TIPS placement is not recommended in the prevention of first VH.**

c.2. Prevention of First Variceal Hemorrhage in Patients With Small Esophageal Varices

The treatment of patients with small varices depends on whether they are at a high risk of hemorrhage (with red wale marks and/or occurring in a CTP-C patient) or whether they lack these characteristics (i.e., low risk of bleeding).[21]

Regarding high-risk small varices, although there is no study that specifically addresses this issue (mainly because it is rare to find patients with high-risk small varices), the recommended treatment is NSBBs, because performing EVL in these varices and defining eradication may be challenging.

Regarding low-risk small varices, there is evidence that shows that NSBBs or carvedilol may delay the growth of small varices,[90,91] but this is controversial.[92,93] Further evidence is required to confirm a benefit from starting therapy at this stage.

Guidance statement

- **NSBB is the recommended therapy for patients with high-risk small EV (Table 3 for doses).**

d) PATIENTS PRESENTING WITH ACUTE ESOPHAGEAL VARICEAL HEMORRHAGE

Patients at this stage are considered decompensated, but 5-year mortality is very different, depending on

whether the patient with cirrhosis presents with VH as an isolated decompensating event (20%) or whether the patient presents with other complications of cirrhosis (ascites or encephalopathy; over 80%).[8]

In this setting, imaging studies aimed at ruling out HCC and portal vein thrombosis (PVT), which can further increase PP and lead to VH and could modify the therapeutic strategy, should be considered or performed.

In this setting, risk stratification is essential. Indeed, there are data to suggest different therapeutic approaches based on this stratification. As mentioned previously, HVPG $\geq$20 mm Hg (measured within 24 hours of admission) is a strong predictor of early rebleeding and death[47] and could be used to stratify risk. However, recognizing that these measurements are unavailable at most centers, a study looking at clinical variables showed a strong association between the CTP class and an HVPG $\geq$20 mm Hg, with more than 80% of CTP-C patients having an HVPG $\geq$20 mm Hg.[27] Recent studies have confirmed the value of CTP class in stratifying risk,[24,25,94] and a recalibrated MELD score has been recently proposed.[23]

The immediate goal of therapy in these patients is to control bleeding, to prevent early recurrence (within 5 days) and prevent 6-week mortality, which is considered, by consensus, the main treatment outcome.[4]

Acute VH is a medical emergency requiring intensive care. As in any patient with any hemorrhage, it is essential to first assess and protect the circulatory and respiratory status of the patient. Volume restitution should be initiated to restore and maintain hemodynamic stability. A recent RCT including patients presenting with GI bleeding showed that a "restrictive" packed red blood cell (PRBC) transfusion strategy (initiating PRBC transfusion at a hemoglobin threshold of 7 g/dL and maintaining it at 7-9 g/dL) was associated with a significant decrease in mortality compared to a "liberal" transfusion strategy (initiating PRBC transfusion at a hemoglobin threshold of 9 g/dL and maintaining it at 9-11 g/dL).[95] In the subgroup of patients with cirrhosis, significantly lower early rebleeding and mortality rates were observed in patients randomized to restrictive PRBC transfusion, particularly in those with CTP class A and B. Notably, HVPG was measured before and after transfusion in some patients, and, though it increased with liberal transfusion, it did not change in those randomized to restrictive transfusion. Transfusion/volume expansion in the individual patient should take into account other factors, such as age, cardiovascular disorders, ongoing hemorrhage, and hemodynamic status.

Regarding correction of coagulopathy, RCTs of recombinant factor VIIa have not shown a clear benefit,[96,97] and therefore correcting the international normalized ratio (INR) by the use of fresh frozen plasma or factor VIIa is not recommended, particularly given that INR is not a reliable indicator of coagulation status in cirrhosis. No recommendations can be given regarding platelet transfusion in patients with VH.

Patients with cirrhosis presenting with GI hemorrhage are at a high risk of developing bacterial infections, and the use of antibiotic prophylaxis has been shown, in RCTs, to lead to a decrease in development of infections, recurrent hemorrhage, and death.[98,99] Studies have recognized that rates of infection and death are low in CTP-A patients with cirrhosis admitted with GI hemorrhage[26,100]; however, there are no prospective studies that evaluate the need of antibiotic prophylaxis in these patients. Regarding the type of antibiotic, intravenous ceftriaxone has been shown to be more effective in preventing infection compared to oral norfloxacin.[101] However, most of the difference was explained by a high rate of infections by quinolone-resistant organisms. The specific antibiotic recommended should be based on individual patient-risk characteristics and local antimicrobial susceptibility patterns, with ceftriaxone (1 g/24 h) being the first choice in patients with advanced cirrhosis, in those on quinolone prophylaxis, and in hospital settings with high prevalence of quinolone-resistant bacterial infections.[4] Norfloxacin is no longer available in the United States and is not available in most inpatient formularies. Therefore, the antibiotic of choice in most centers is intravenous ceftriaxone at a dose of 1 g every 24 hours. Duration of antibiotic prophylaxis is short term, for a maximum of 7 days.

A meta-analysis of 30 RCTs shows that the use of vasoactive agents in acute VH is associated with lower 7-day all-cause mortality and lower transfusion requirements[102]; therefore, they should be started as soon as possible, together with antibiotics and before diagnostic endoscopy. All vasoactive drugs used in the control of acute hemorrhage are used in intravenous infusion. A recent study comparing the three most-utilized worldwide (SMT, octreotide, and terlipressin) found no significant differences among them, although terlipressin was used at doses lower than recommended.[103] Octreotide is the only vasoactive drug available in the United States, and in a meta-analysis of 11 trials, it was shown to significantly improve control of acute hemorrhage.[102] Table 4 shows the recommended doses, therapeutic goals, and follow-up procedures for vasoactive drugs used in acute VH.

TABLE 4. Vasoactive Agents Used in the Management of Acute Variceal Hemorrhage

Drug	Recommended Dose	Duration
Octreotide (SMT analogue)	Initial IV bolus of 50 micrograms (can be repeated in first hour if ongoing bleeding) Continuous IV infusion of 50 μg/hr	2-5 days
Vasopressin	Continuous IV infusion: 0.2-0.4 U/min; can be increased to 0.8 U/min It should always be accompanied by IV nitroglycerin at a starting dose of 40 μg/min, which can be increased to a maximum of 400 μg/min, adjusted to maintain a systolic blood pressure 90 mm Hg.	24 hours
SMT	Initial IV bolus 250 μg (can be repeated in the first hour if ongoing bleeding) Continuous IV infusion of 250-500 μg/h	2-5 days
Terlipressin (VP analogue)	Initial 48 hours: 2 mg IV every 4 hours until control of bleeding Maintenance: 1 mg IV every 4 hours to prevent rebleeding	2-5 days

Only one of these four agents should be used.
Abbreviations: IV, intravenous; SMT, somatostatin; VP, vasopressin.

Endoscopy is done as soon as possible and not more than 12 hours after presentation. If a variceal source is confirmed, EVL should be performed. The diagnosis of VH is considered certain when active bleeding from a varix is observed or when a sign of recent bleeding, such as a "white nipple," is observed. VH should be inferred when varices are the only lesion found, and either blood is present in the stomach or endoscopy is performed after 24 hours of hemorrhage.

Once endoscopy and EVL have been performed, RCTs have shown that, compared to standard therapy, "early" (preemptive) TIPS (placed within 72 hours of admission) is associated with significantly lower treatment failure and mortality rates in carefully selected high-risk patients. These have been defined in one trial (which used uncovered TIPS stents) as those with an HVPG >20 mm Hg,[104] and in a second trial (which used currently recommended covered TIPS stents) as those with CTP class C cirrhosis with a score of 10-13 and those with CTP class B with active bleeding on endoscopy despite intravenous vasoactive drug therapy.[105] The latter trial had many exclusion criteria, including CTP class A, CTP class B without active bleeding at endoscopy, CTP-C patients with a score of 14 and 15 points, age > 75 years, HCC outside Milan criteria, a creatinine level greater than 3 mg/dL, previous combination pharmacological plus endoscopic treatment to prevent rebleeding, bleeding from isolated gastric or ectopic varices, total PVT, and heart failure. Patients included in the study constituted <20% of those admitted for VH. Notably, observational studies have not confirmed the effect of early TIPS on survival,[106,107] and further studies are necessary.

Patients who do not belong to the "high-risk" categories defined above should continue standard therapy with vasoactive drugs continued for up to 5 days depending on control of bleeding and severity of liver disease. Persistent bleeding, or severe rebleeding despite combined pharmacological and endoscopic therapy, is best managed by polytetrafluoroethylene-covered TIPS. If rebleeding is modest, a second session of endoscopy therapy can be attempted.

Up to 20% of VH episodes can be refractory to standard therapy and are associated with a high mortality. A "bridge" therapy may be necessary in order to acutely control hemorrhage until a more definitive therapy, such as TIPS, can be performed. Balloon tamponade is still used as bridge therapy and provides hemostasis in up to 80% of patients, but is associated with a high rate of severe adverse events and a mortality rate near 20%.[1] Balloon tamponade should not exceed 24 hours.

A recent small, multicenter RCT compared balloon tamponade to endoscopically placed self-expandable metal stents in patients with cirrhosis and VH refractory to medical and endoscopic treatment. Although no differences in survival could be demonstrated, control of bleeding was significantly greater and side effects were significantly lower with metal stents.[108] Additionally, these stents can stay in place for up to 7 days, allowing more time for resuscitation and plans for definitive therapy.

Guidance statements

- **PRBC transfusion should be done conservatively, starting to transfuse when the hemoglobin reaches a threshold of around 7 g/dL with the goal of maintaining it between 7 and 9 g/dL.**
- **Short-term (maximum 7 days) antibiotic prophylaxis should be instituted in any patient with cirrhosis and GI hemorrhage.**

- **Intravenous ceftriaxone 1 g/24 h is the antibiotic of choice and should be used for a maximum of 7 days (consider discontinuing when hemorrhage has resolved and vasoactive drugs discontinued).**
- **Vasoactive drugs (SMT or its analogue, octreotide; VP or its analogue, terlipressin) should be initiated as soon as VH is suspected (Table 4 for recommended doses and schedules).**
- **EGD should be performed within 12 hours of admission and once the patient is hemodynamically stable.**
- **If a variceal source is confirmed/suspected, EVL should be performed.**
- **In patients at high risk of failure or rebleeding (CTP class C cirrhosis or CTP class B with active bleeding on endoscopy) who have no contraindications for TIPS, an "early" (preemptive) TIPS within 72 hours from EGD/EVL may benefit selected patients.**
- **For patients in whom an early TIPS is not performed, intravenous vasoactive drugs should be continued for 2-5 days and NSBBs initiated once vasoactive drugs are discontinued. Rescue TIPS is indicated in these patients if hemorrhage cannot be controlled or if bleeding recurs despite vasoactive drugs+EVL.**
- **In patients in whom TIPS is performed successfully, intravenous vasoactive drugs can be discontinued.**

e) PATIENTS WHO HAVE RECOVERED FROM AN EPISODE OF ACUTE ESOPHAGEAL VARICEAL HEMORRHAGE

This clinical setting was previously described as "secondary prophylaxis of variceal hemorrhage." However, as mentioned previously, therapies have to be taken in the context of the presence or absence of other complications of cirrhosis. In patients with a low risk of death (those with VH as the sole complication of cirrhosis), the objective of therapy should be the prevention of an additional complication, including variceal rebleeding, whereas in patients at a high risk of death (those with VH and other decompensating events), the objective of therapy should be to improve survival.[4]

Given that these specific objectives have not been explored as main endpoints in clinical trials until now, the following recommendations are only pertinent with regard to prevention of recurrent VH. Patients who recover from the first episode of VH have a high rebleeding risk (60% in the first year), with a mortality of up to 33%. Therapy to prevent rebleeding is therefore mandatory in these patients and should be instituted before the patients is discharged from the hospital.

Patients who had a TIPS performed during the acute episode do not require specific therapy for PH or varices, but should be referred for transplant evaluation. TIPS patency should be assessed by Doppler ultrasound every 6 months (at the same time as ultrasound is being performed for HCC screening). First-line therapy for all other patients (the majority) is the combination of NSBBs (propranolol or nadolol)+EVL. A recent meta-analysis comparing combination therapy to monotherapy with EVL or drug therapy has demonstrated that combination therapy is significantly more effective than EVL alone in preventing all-source GI hemorrhage. However, combination therapy is only marginally more effective than drug therapy (NSBB+nitrates) alone, with a tendency for an increased survival with drugs alone.[109] This suggests that pharmacological therapy is the cornerstone of combination therapy. Therefore, if NSBB are not tolerated, TIPS should be considered, particularly if the patient has another complication (e.g., ascites) that could benefit from TIPS.

The combination of NSBBs plus low-dose isosorbide mononitrate (ISMN) has a greater PP-reducing effect than NSBBs alone, but rate of side effects is higher because of the added ones associated with ISMN, specifically headache and lightheadedness. In a meta-analysis, the combination of NSBB and ISMN was no different than NSBB alone regarding overall rebleeding or mortality, but had a higher rate of side effects.[110]

In the setting of secondary prophylaxis of VH, carvedilol has only been compared to EVL alone[111] or to NSBB+ISMN,[112] but has not been compared to standard of care with the combination of NSBB+EVL. Therefore, there are not enough data to recommend carvedilol in the prevention of rebleeding. Additionally, carvedilol, particularly at doses >12.5 mg/day, may decrease arterial pressure[42] and should not be used in patients with refractory ascites (even in the setting of primary prophylaxis).

A recent multicenter, placebo-controlled RCT showed that the addition of simvastatin (40 mg per oral every day) was not associated with a reduction in

TABLE 5. Treatments for the Prevention of Recurrent Esophageal Variceal Hemorrhage

Therapy	Recommended Dose	Therapy Goals	Maintenance/Follow-up
Propranolol	• 20-40 mg orally *twice* a day • Adjust every 2-3 days until treatment goal is achieved • Maximal daily dose: ○ 320 mg/day in patients without ascites ○ 160 mg/day in patients with ascites	• Resting heart rate of 55-60 beats per minute • Systolic blood pressure should not decrease <90 mm Hg	• At every outpatient visit make sure that heart rate is on target • Continue indefinitely
Nadolol	• 20-40 mg orally *once* a day • Adjust every 2-3 days until treatment goal is achieved • Maximal daily dose: ○ 160 mg/day in patients without ascites ○ 80 mg/day in patients with ascites	• Resting heart rate of 55-60 beats per minute • Systolic blood pressure should not decrease <90 mm Hg	• At every outpatient visit make sure that heart rate is on target • Continue indefinitely
EVL	• Every 1-4 weeks until the eradication of varices	• Variceal eradication (no further ligation possible)	• First EGD performed 3-6 months after eradication and every 6-12 months thereafter

The combination of either propranolol or nadolol *plus* EVL is recommended. Carvedilol is not recommended in this setting.

rebleeding (compared to placebo), but was associated with a significant improvement in survival, mainly related to a decrease in deaths from bleeding or infections.[113] However, there was a higher-than-expected incidence of rhabdomyolysis, limited to patients with severe liver dysfunction.

TIPS is the treatment of choice in patients that fail first-line therapy to prevent rebleeding (NSBB+EVL). Until recently, all trials comparing TIPS and endoscopic therapy had used uncovered TIPS stents.[114] In a recent multicenter RCT, TIPS (using the currently recommended covered stents) was compared to EVL or glue injection plus NSBBs and showed a significantly lower rebleeding rate (0% vs. 29%) in patients treated with covered TIPS with no differences in survival and with a higher incidence of early encephalopathy in the TIPS group.[115]

The lowest rebleeding rates are observed in patients on secondary prophylaxis who are HVPG responders (defined as a reduction in HVPG below 12 mm Hg or > 20% from baseline).[28] Therefore, HVPG-guided therapy performed in centers where HVPG measurements are readily available would be a reasonable strategy. A recent RCT of covered TIPS versus HVPG-guided therapy (propranolol and isosorbide mononitrate) showed lower rebleeding rates in patients randomized to TIPS (7% versus 26%) without differences in survival and with a higher incidence of encephalopathy in the TIPS group.[116]

Table 5 shows the recommended doses, therapeutic goals, and follow-up procedures for each of the first-line recommended therapies.

Guidance statements

- **Combination of NSBB+EVL is first-line therapy in the prevention of rebleeding (Table 5 for recommended doses and schedules).**
- **Patients who have a TIPS placed successfully during the acute episode do not require NSBBs or EVL.**
- **TIPS is the recommended rescue therapy in patients who experience recurrent hemorrhage despite combination therapy NSBB+EVL.**

G. Gastric Varices

Gastric varices (GV) are present in around 20% of patients with cirrhosis. Sarin's classification is the most commonly used for risk stratification and management of GV.[117] GOV type 1 (GOV1) are EV extending below the cardia into the lesser curvature and are the most common (75% of GV). GOV type 2 (GOV2) are those extending into the fundus. Isolated GV type 1 (IGV1) are located in the fundus (IGV1). GOV2 and IGV1 are commonly referred to as "cardiofundal varices." Isolated GV type 2 (IGV2) are located elsewhere in the stomach, but are extremely infrequent in

patients with cirrhosis. The main factors associated with a higher risk of bleeding are localization (IGV1 > GOV2 > GOV1), large size, presence of red spots, and severity of liver dysfunction.[117,118]

Cardiofundal varices are much more frequent in patients with portal vein and/or splenic vein thrombosis, and the finding of these varices should prompt imaging to investigate the presence of such thromboses. In patients with bleeding cardiofundal varices, and because endovascular obliteration is an option in those with a large gastro- or splenorenal collateral, cross-sectional vascular imaging is preferred given that it would investigate both thrombosis and the presence of such collaterals and would guide management accordingly.

The evidence to support recommendations for management of gastric VH is much less robust than that for EV. There are only a few controlled trials available, including a small sample size and, in most instances, without adequate stratification according to the type of varices or severity of liver disease.

a) PREVENTION OF FIRST HEMORRHAGE FROM GASTRIC VARICES

Only one randomized trial has been published on the primary prevention of gastric VH. This study included 89 patients with large (≥10 mm) GOV2 and IGV1 that were randomized to endoscopic injection of cyanoacrylate (glue), NSBBs, and observation.[119] The number of patients with IGV1 was small (15%). Cyanoacrylate injection was associated with lower bleeding rates (10%) than NSBBs (38%) and observation (53%). Survival was higher in the cyanoacrylate group (93%) compared to observation (74%), but no different from those on NSBBs (83%). Firm recommendations cannot be derived from this trial. The least invasive treatment is NSBBs, and this could be recommended because, as mentioned previously, they could have beneficial effects in preventing other complications of cirrhosis.

Although no studies have specifically evaluated the efficacy of TIPS in preventing first hemorrhage from cardiofundal varices, results from trials of prophylactic surgical shunt therapy show a significantly higher rate of encephalopathy, and a tendency for a higher mortality in patients randomized to shunt surgery. Therefore, TIPS is not recommended in this setting.[89] The efficacy of BRTO in preventing first hemorrhage in patients with cardiofundal varices has not been studied, and therefore this therapy cannot be recommended either for primary prophylaxis.

No studies have assessed primary prevention of bleeding from GOV1 varices. These are commonly managed following guidelines for EV (see above).

Guidance statements

- **For prevention of first VH from GOV2 or IGV1, NSBBs can be used, although the data are not as strong as for EV.**
- **Prevention of first bleeding from GOV1 varices may follow the recommendations for EV.**
- **Neither TIPS nor BRTO are recommended to prevent first hemorrhage in patients with fundal varices that have not bled.**

b) MANAGEMENT OF ACUTE HEMORRHAGE FROM GASTRIC VARICES

The initial treatment of gastric VH is similar to that of esophageal VH (volume resuscitation, vasoactive drugs, and antibiotics before diagnostic endoscopy).

In case of massive bleeding, balloon tamponade with the Linton-Nachlas tube may serve as a bridge to other treatments. If using the Sengstaken-Blakemore or Minnesota tubes, inflation of only the gastric balloon and anchoring it against the gastroesophageal junction could be sufficient to produce adequate tamponade.

b.1. Endoscopic Therapy

Meta-analysis of three RCTs comparing cyanoacrylate injection versus EVL shows that both therapies are equally effective for initial hemostasis, but cyanoacrylate injection is associated with significantly lower rebleeding rates.[120] The overall quality of the evidence is low given small sample sizes, and the meta-analysis was dominated by the larger study including only GOV1 varices.[121] In addition, EVL should only be performed on small GV in which both the mucosal and contralateral wall of the vessel can be suctioned into the ligator; otherwise, the band will fall off in several days, leaving an ulcer overlying the vessel, which can result in catastrophic rebleeding. Other endoscopic tools are rapidly emerging that may provide far greater safety and efficacy, such as the endoscopic ultrasound–guided insertion of coils and cyanoacrylate.[122]

The cyanoacrylate used in randomized trials has been N-butyl-2-cyanoacrylate; 2-octyl cyanoacrylate is an alternative with longer polymerization time[123] and has

been used with success in acute gastric VH.[124] None of them is specifically approved for treating gastric VH in the United States. The technique has been recently reviewed by the ASGE in a technical report.[125]

b.2. Transjugular Intrahepatic Portosystemic Shunt

TIPS is very effective in the treatment of bleeding GV, with more than a 90% success rate for initial hemostasis.[126] It frequently requires additional embolization of spontaneous collaterals feeding the varices. TIPS has not been compared to endoscopic cyanoacrylate injection or to variceal ligation for the initial control of bleeding. In centers with expertise in cyanoacrylate injection, it would be reasonable to reserve TIPS for failures of medical (intravenous vasoconstrictors) plus endoscopic (glue) therapy. However, in the case of fundal varices, which have a higher early rebleeding rate, TIPS should be considered earlier than for other types of varices.

Guidance statements

- **Patients with acute bleeding from GV should be initially managed in a similar fashion to those bleeding from EV (using a restrictive transfusion policy, vasoactive drug infusion, and antibiotic prophylaxis)**.
- **In patients bleeding from GOV1 varices, either EVL (if technically feasible) or cyanoacrylate glue injection, if available, are the recommended endoscopic treatments**.
- **TIPS is the treatment of choice in the control of bleeding from cardiofundal varices (GOV2 or IGV1)**.
- **Cyanoacrylate glue injection is an option for cases in which TIPS is not technically feasible, but it is not approved for treatment of GV in the United States and should be performed only in centers where the expertise is available**.

c) PREVENTION OF REBLEEDING

c.1. Endoscopic Therapy and Nonselective Beta-Blockers

In one RCT, repeated cyanoacrylate injection was superior to NSBB in the prevention of rebleeding and mortality in patients with cardiofundal varices.[127] In another trial, also in patients with cardiofundal varices, addition of NSBBs to cyanoacrylate injection did not improve the rebleeding or mortality rates compared to cyanoacrylate alone.[128]

c.2. Transjugular Intrahepatic Portosystemic Shunt

A single randomized trial including patients with GOV1 and GOV2 varices showed that TIPS is more effective than glue injection in preventing rebleeding,[129] but with higher rate of encephalopathy and without differences in survival.

c.3. Balloon Occluded Retrograde Transvenous Obliteration

BRTO is a procedure for treatment of fundal varices associated with a large gastro-/splenorenal collateral.[130] The technique involves retrograde cannulation of the left renal vein by the jugular or femoral vein, followed by balloon occlusion and slow infusion of sclerosant to obliterate the gastro-/splenorenal collateral and fundal varices.[44,131] Several variations of the technique exist, such as balloon-occluded antegrade transvenous obliteration[132] or occlusion of the collateral by the placement of a vascular plug[133] or coils.[134] BRTO has the theoretical advantage over TIPS that it does not divert portal blood inflow from the liver. On the other hand, BRTO and its variations might increase portal pressure and might worsen complications, such as ascites or bleeding from EV. For this reason, some centers will measure portal pressure and place a TIPS in cases in which the HVPG exceeds 12 mm Hg post-BRTO. No randomized trials have compared BRTO with other therapies.

Guidance statements

- **In patients who have recovered from a GOV1 hemorrhage, the combination of NSBBs and endoscopic variceal therapy (EVL or cyanoacrylate injection) is the first-line therapy to prevent rebleeding**.
- **In patients who have recovered from GOV2 or IGV1 hemorrhage, TIPS or BRTO are first-line treatments in the prevention of rebleeding**.
- **Cyanoacrylate glue injection is an option for cases in which TIPS or BRTO are not technically feasible, but it is not approved for the treatment of GV in the United States and should be performed only in centers where the expertise is available**.

H. Ectopic Varices

Bleeding from ectopic varices is very rare in cirrhosis, but it is a significant source of bleeding in patients with prehepatic PH.[135,136] Localization and anatomy are heterogeneous, which makes standardization of treatment difficult, and therefore cases should be evaluated/treated on a case-by-case basis and based on vascular anatomy. Diagnosis can be made with a thin-slice contrast-enhanced CT in the portal venous phase, using large-volume diluted water-soluble oral contrast. The most frequent locations are surgical stomas, duodenum, jejuno-ileum, and colon. Management requires a good definition of the vascular supply and local hemodynamics of the varices and a multidisciplinary approach involving endoscopists, hepatologists, interventional radiologists and surgeons. Treatment options include endoscopic therapy, mostly with cyanoacrylate injection or endosonographic coil placement, TIPS with or without collateral embolization, and BRTO. In the case of stomal varices, direct injection of sclerosant agents or cyanoacrylate under radiographic guidance can be very successful.

Guidance statement

- **The management of ectopic varices requires a thorough knowledge of the vascular supply to the varices and a multidisciplinary approach. Options are ligation, cyanoacrylate injection, endosonographic coil placement, TIPS with or without embolization, and BRTO**.

I. Special Populations

a) PATIENTS WITH REFRACTORY ASCITES OR AFTER SPONTANEOUS BACTERIAL PERITONITIS

Recent observational studies raised concerns regarding the use of NSBBs in patients with advanced cirrhosis, either with refractory ascites or after an episode of spontaneous bacterial peritonitis (SBP). In the first study, the effect of NSBBs on mortality was prospectively assessed in 151 consecutive patients admitted for refractory ascites.[137] After adjustment for severity of liver disease, NSBB use was associated with increased mortality. Notably, patients on NSBBs had a significantly lower systolic pressure compared to those not on NSBBs. A follow-up small crossover study showed that, while on NSBBs, a larger percentage of patients developed postparacentesis circulatory dysfunction than while off NSBBs.[138] A second retrospective study showed that NSBBs improved survival in patients with ascites, but in a subanalysis limited to those surviving an episode of SBP episode, NSBBs worsened survival and had a higher risk for hepatorenal syndrome (HRS).[139] Again, patients on NSBBs had lower blood pressure.

These concepts have been challenged in three subsequent studies assessing large cohorts of patients with ascites,[140-142] studies that have shown either no differences[141] or even improved survival[140,142] in patients treated with NSBBs, including patients with refractory ascites. An additional study showed that ongoing treatment with NSBBs was associated with improved survival in patients with acute-on-chronic liver failure.[143] In these studies, MAP was not significantly different between patients on NSBB and those not on them.

Two recent observational studies found an association of the dose of NSBBs and outcomes. The first showed that in patients with decompensated cirrhosis, doses of propranolol above 160 mg/day were associated with worse survival, whereas doses up to 160 mg/day were associated with an improved survival.[142] In the second study, focused on patients with SBP, doses <160 mg/day of propranolol were associated with improved survival after adjustment for confounders, whereas doses of 160 mg/day or above were not.[144]

In summary, current evidence from observational studies does not support a harmful effect of NSBBs in most patients with decompensated cirrhosis. In these patients, the dose of NSBBs should be carefully titrated. In patients with refractory ascites or SBP, high doses of NSBBs should be avoided. NSBB dose should be reduced or discontinued in patients with refractory ascites with signs of severe circulatory dysfunction, such as severe hypotension (systolic blood pressure < 90 mm Hg), hyponatremia (serum sodium < 130 meq/L), or unexplained deterioration in renal function.[4] NSBBs might be reintroduced after correction of renal function/circulatory state. This is particularly important when NSBBs are used to prevent recurrent VH.

Guidance statements

- **Refractory ascites and SBP are *not* absolute contraindications for treatment with NSBBs. In these patients, high doses of NSBBs (over 160 mg/day of propranolol or over 80 mg/day of nadolol) should be avoided, given that they might be associated with worse outcomes**.

- **In patients with refractory ascites and severe circulatory dysfunction (systolic blood pressure < 90 mm Hg, serum sodium <130 meq/L, or HRS), the dose of NSBBs should be decreased or the drug temporarily held. NSBBs might be reintroduced if circulatory dysfunction improves**.

b) PREVENTION OF REBLEEDING IN PATIENTS EXPERIENCING THE FIRST VARICEAL HEMORRHAGE WHILE ON PRIMARY PROPHYLAXIS WITH NON-SELECTIVE BETA-BLOCKERS OR ENDOSCOPIC VARICEAL LIGATION

The widespread use of primary prophylaxis with NSBBs or EVL has led to an increasing number of patients with cirrhosis who experience their first episode of VH while on primary prophylactic therapy (NSBBs or EVL). These patients, however, have been excluded in most trials evaluating current standard of care in the prevention of rebleeding. Therefore, the best approach to treat these patients is unknown. A recent cohort study assessing 89 patients on standard secondary prophylaxis showed that rebleeding and mortality were significantly higher in patients who had bled while on prophylactic NSBBs compared to those that experienced VH not having been on NSBBs.[145] These findings suggest that patients who bleed while on primary prophylaxis may need more-aggressive therapy, such as TIPS. In the absence of RCTs, the optimal therapeutic strategy in this setting remains conjectural.

Guidance statement

- **Patients failing primary prophylaxis for VH may be treated with the combination of NSBBs and EVL or, alternatively, with TIPS. Randomized trials are required in this group of patients to clarify the best therapeutic strategy**.

c) PREVENTION AND TREATMENT OF VARICEAL HEMORRHAGE IN PATIENTS WITH HEPATOCELLULAR CARCINOMA

Most randomized trials for the prevention and treatment of VH have excluded patients with HCC, and the few including HCC patients excluded those with advanced disease. Therefore, the optimal treatment for these patients remains unknown. Although observational data suggest that the risk of bleeding and prognosis of the bleeding episode might be worse in these patients,[146-148] there are no data to suggest a decreased efficacy of treatments to prevent bleeding (NSBBs, EVL, or TIPS if technically feasible) as compared with no intervention. In a recent observational study, lack of secondary prophylaxis was frequent in patients with HCC recovering from acute VH, and this was independently associated with mortality, after adjusting for HCC stage and liver dysfunction.[148] This suggests that these patients should receive the same secondary prophylaxis as patients without HCC, including those who have PVT (tumoral or bland). In patients with advanced HCC, therapeutic decisions related to VH should be framed within the context of the end-of-life care plan of the patient.

Guidance statement

- **Prevention and treatment of acute VH in patients with HCC should follow the same principles as those for patients without HCC**.

J. Suggestions for Future Research

The following are important areas in the diagnosis and treatment of varices and variceal hemorrhage for which additional research/data are needed:

1. The role of noninvasive tests (e.g., liver stiffness, spleen stiffness) in the diagnosis of CSPH in patients with etiologies other than viral/alcoholic cirrhosis.
2. The role of noninvasive tests in evaluating hemodynamic response to different therapies and their relationship to clinical outcomes.
3. Prospective studies evaluating the effect of therapies that act on pathophysiological mechanisms of PH in the prevention of clinical outcomes other than varices/VH.
4. Effects of antifibrotic drugs preventing disease progression in patients with compensated cirrhosis.
5. Role of gut microbiota modulating the hemodynamic abnormalities of cirrhosis and PH and the response to medical therapy.
6. Clarify the role of preemptive ("early") TIPS in the management of acute VH, refining the target population that will benefit from this treatment.

7. Data on clinical outcomes for statins and other potential targets not yet used clinically in this setting (e.g., farnesoid X receptor agonists, enoxaparin).
8. Optimal prevention and treatment of bleeding from cardiofundal varices.

Acknowledgments: This Practice Guidance was developed under the direction of the AASLD Practice Guidelines Committee, which approved the scope of the guidance and provided the peer review. Members of the Committee include Raphael B. Merriman, M.D., F.A.C.P., F.R.C.P.I. (Chair), Tram T. Tran, M.D., F.A.A.S.L.D. (Vice-Chair), Michael W. Fried, M.D., F.A.A.S.L.D. (Board Liaison), Jawad Ahmad, M.D., F.A.A.S.L.D., Joseph Ahn, M.D., Fredric Gordon, M.D., F.A.A.S.L.D., Simon P. Horslen, M.D., Whitney E. Jackson, M.D., Fasiha Kanwal, M.D., M.S.H.S., Michael D. Leise, M.D., Jacqueline G. O'Leary, M.D., Michael L. Schilsky, M.D., F.A.A.S.L.D., Amit Singal, M.D., James R. Spivey, M.D., Helen S. Te, M.D., F.A.A.S.L.D., and Michael Volk, M.D.

REFERENCES

1) Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology 2007;46:922-938.
2) Garcia-Tsao G, Bosch J, Groszmann RJ. Portal hypertension and variceal bleeding—unresolved issues. Summary of an American Association for the Study of Liver Diseases and European Association for the Study of the Liver Single-Topic Conference. Hepatology 2008;47:1764-1772.
3) de Franchis R; Baveno V Faculty. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2010;53:762-768.
4) de Franchis R; Baveno V Faculty. Expanding consensus in portal hypertension. Report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743-752.
5) D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis. A systematic review of 118 studies. J Hepatol 2006;44:217-231.
6) Scaglione S, Kliethermes S, Cao G, Shoham D, Durazo R, Luke A, et al. The epidemiology of cirrhosis in the United States: a population-based study. J Clin Gastroenterol 2015;49:690-696.
7) Garcia-Tsao G. Natural history of cirrhosis. In: Cárdenas A, Keaveny A, eds. Complications of Cirrhosis. Cham, Switzerland: Springer International; 2015.
8) D'Amico G, Pasta L, Morabito A, D'Amico M, Caltagirone M, Malizia G, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther 2014;39:1180-1193.
9) Blasco A, Forns X, Carrion JA, Garcia-Pagan JC, Gilabert R, Rimola A, et al. Hepatic venous pressure gradient identifies patients at risk of severe hepatitis C recurrence after liver transplantation. Hepatology 2006;43:492-499.
10) **Groszmann RJ, Garcia-Tsao G,** Bosch J, Grace ND, Burroughs AK, Planas R, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med 2005;353:2254-2261.
11) Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007;133:481-488.
12) Bruix J, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients. Prognostic value of preoperative portal pressure. Gastroenterology 1996;111:1018-1022.
13) Ripoll C, Groszmann RJ, Garcia-Tsao G, Bosch J, Grace N, Burroughs A, et al. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. J Hepatol 2009;50:923-928.
14) Lebrec D, De Fleury P, Rueff B, Nahum H, Benhamou JP. Portal hypertension, size of esophageal varices, and risk of gastrointestinal bleeding in alcoholic cirrhosis. Gastroenterology 1980;79:1139-1144.
15) Garcia-Tsao G, Groszmann RJ, Fisher RL, Conn HO, Atterbury CE, Glickman M. Portal pressure, presence of gastroesophageal varices and variceal bleeding. Hepatology 1985;5:419-424.
16) Bruno S, Zuin M, Crosignani A, Rossi S, Zadra F, Roffi L, et al. Predicting mortality risk in patients with compensated HCV-induced cirrhosis: a long-term prospective study. Am J Gastroenterol 2009;104:1147-1158.
17) Zipprich A, Garcia-Tsao G, Rogowski S, Fleig WE, Seufferlein T, Dollinger MM. Prognostic indicators of survival in patients with compensated and decompensated cirrhosis. Liver Int 2012;32:1407-1414.
18) Pagliaro L, D'Amico G, Pasta L, Politi F, Vizzini G, Traina M, et al. Portal hypertension in cirrhosis: natural history. In: Bosch J, Groszmann RJ, eds. Portal Hypertension. Pathophysiology and Treatment. Oxford, UK: Blackwell Scientific; 1994:72-92.
19) Kovalak M, Lake J, Mattek N, Eisen G, Lieberman D, Zaman A. Endoscopic screening for varices in cirrhotic patients: data from a national endoscopic database. Gastrointest Endosc 2007;65:82-88.
20) Merli M, Nicolini G, Angeloni S, Rinaldi V, DeSantis A, Merkel C, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. J Hepatol 2003;38:266-272.
21) North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med 1988;319:983-989.
22) D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. Semin Liver Dis 1999;19:475-505.
23) Reverter E, Tandon P, Augustin S, Turon F, Casu S, Bastiampillai R, et al. A MELD-based model to determine risk of mortality among patients with acute variceal bleeding. Gastroenterology 2014;146:412-419.
24) Amitrano L, Guardascione MA, Manguso F, Bennato R, Bove A, DeNucci C, et al. The effectiveness of current acute variceal bleed treatments in unselected cirrhotic patients: refining short-

term prognosis and risk factors. Am J Gastroenterol 2012;107: 1872-1878.
25) Fortune B, Garcia-Tsao G, Ciarleglio M, Deng Y, Fallon MB, Sigal S, et al.; Vapreotide Study Group. Child-Turcotte-Pugh Class is best at stratifying risk in variceal hemorrhage: analysis of a U.S. multi-center prospective study. J Clin Gastroenterol 2016 Oct 24. doi: 10.1097/MCG.0000000000000733. [Epub ahead of print]
26) **Tandon P**, **Abraldes JG**, Keough A, Bastiampillai R, Jayakumar S, Carbonneau M, et al. Risk of bacterial infection in patients with cirrhosis and acute variceal hemorrhage, based on Child-Pugh class, and effects of antibiotics. Clin Gastroenterol Hepatol 2015;13:1189-1196.
27) Abraldes JG, Villanueva C, Banares R, Aracil C, Catalina MV, Garci AP, et al. Hepatic venous pressure gradient and prognosis in patients with acute variceal bleeding treated with pharmacologic and endoscopic therapy. J Hepatol 2008;48:229-236.
28) Bosch J, Garcia-Pagan JC. Prevention of variceal rebleeding. Lancet 2003;361:952-954.
29) Everhart JE, Lok AS, Kim HY, Morgan TR, Lindsay KL, Chung RT, et al. Weight-related effects on disease progression in the hepatitis C antiviral long-term treatment against cirrhosis trial. Gastroenterology 2009;137:549-557.
30) Berzigotti A, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Morillas R, et al. Obesity is an independent risk factor for clinical decompensation in patients with cirrhosis. HEPATOLOGY 2011;54:555-561.
31) Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet 2013;381:468-475.
32) Monto A, Patel K, Bostrom A, Pianko S, Pockros P, McHutchison JG, et al. Risks of a range of alcohol intake on hepatitis C-related fibrosis. HEPATOLOGY 2004;39:826-834.
33) Hutchinson SJ, Bird SM, Goldberg DJ. Influence of alcohol on the progression of hepatitis C virus infection: a meta-analysis. Clin Gastroenterol Hepatol 2005;3:1150-1159.
34) Bosch J, Groszmann RJ, Shah VH. Evolution in the understanding of the pathophysiological basis of portal hypertension: how changes in paradigm are leading to successful new treatments. J Hepatol 2015;62(1 Suppl):S121-S130.
35) Iwakiri Y, Groszmann RJ. Vascular endothelial dysfunction in cirrhosis. J Hepatol 2007;46:927-934.
36) Bhathal PS, Grossman HJ. Reduction of the increased portal vascular resistance of the isolated perfused cirrhotic rat liver by vasodilators. J Hepatol 1985;1:325-337.
37) Abraldes JG, Rodriguez-Vilarrupla A, Graupera M, Zafra C, Garcia-Caldero H, Garcia-Pagan JC, et al. Simvastatin treatment improves liver sinusoidal endothelial dysfunction in CCl4 cirrhotic rats. J Hepatol 2007;46:1040-1046.
38) Fernandez M, Vizzutti F, Garcia-Pagan JC, Rodes J, Bosch J. Anti-VEGF receptor-2 monoclonal antibody prevents portal-systemic collateral vessel formation in portal hypertensive mice. Gastroenterology 2004;126:886-894.
39) Sikuler E, Kravetz D, Groszmann RJ. Evolution of portal hypertension and mechanisms involved in its maintenance in a rat model. Am J Physiol 1985;248:G618-G625.
40) Kroeger RJ, Groszmann RJ. Effect of selective blockade of beta-2 adrenergic receptors on portal and systemic hemodynamics in a portal hypertensive rat model. Gastroenterology 1985; 88:896-900.
41) Garcia-Tsao G, Grace N, Groszmann RJ, Conn HO, Bermann MM, Patrick MJ, et al. Short term effects of propranolol on portal venous pressure. HEPATOLOGY 1986;6:101-106.
42) Sinagra E, Perricone G, D'Amico M, Tine F, D'Amico G. Systematic review with meta-analysis: the haemodynamic effects of carvedilol compared with propranolol for portal hypertension in cirrhosis. Aliment Pharmacol Ther 2014;39:557-568.
43) Villanueva C, Albillos A, Genesca J, Abraldes JG, Calleja JL, Aracil C, et al. Development of hyperdynamic circulation and response to beta-blockers in compensated cirrhosis with portal hypertension. HEPATOLOGY 2016;63:197-206.
44) Saad WE. Endovascular management of gastric varices. Clin Liver Dis 2014;18:829-851.
45) Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: anything worth doing should be done right. HEPATOLOGY 2004;39:280-283.
46) Merkel C, Bolognesi M, Sacerdoti D, Bombonato G, Bellini B, Bighin R, et al. The hemodynamic response to medical treatment of portal hypertension as a predictor of clinical effectiveness in the primary prophylaxis of variceal bleeding in cirrhosis. HEPATOLOGY 2000;32:930-934.
47) Moitinho E, Escorsell A, Bandi JC, Salmeron JM, Garcia-Pagan JC, Rodes J, et al. Prognostic value of early measurements of portal pressure in acute variceal bleeding. Gastroenterology 1999;117:626-631.
48) Ripoll C, Banares R, Rincon D, Catalina MV, Lo IO, Salcedo M, et al. Influence of hepatic venous pressure gradient on the prediction of survival of patients with cirrhosis in the MELD era. HEPATOLOGY 2005;42:793-801.
49) Berzigotti A, Seijo S, Arena U, Abraldes JG, Vizzutti F, Garcia-Pagan JC, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. Gastroenterology 2013;144:102-111.
50) Vilgrain V, Lebrec D, Menu Y, Scherrer A, Nahum H. Comparison between ultrasonographic signs and the degree of portal hypertension in patients with cirrhosis. Gastrointest Radiol 1990;15:218-222.
51) Berzigotti A, Piscaglia F. Ultrasound in portal hypertension—part 1. Ultraschall Med 2011;32:548-568.
52) Berzigotti A, Piscaglia F. Ultrasound in portal hypertension—part 2—and EFSUMB recommendations for the performance and reporting of ultrasound examinations in portal hypertension. Ultraschall Med 2012;33:8-32.
53) Kim BK, Han KH, Park JY, Ahn SH, Kim JK, Paik YH, et al. A liver stiffness measurement-based, noninvasive prediction model for high-risk esophageal varices in B-viral liver cirrhosis. Am J Gastroenterol 2010;105:1382-1390.
54) Shi KQ, Fan YC, Pan ZZ, Lin XF, Liu WY, Chen YP, et al. Transient elastography: a meta-analysis of diagnostic accuracy in evaluation of portal hypertension in chronic liver disease. Liver Int 2013;33:62-71.
55) Castera L, Pinzani M, Bosch J. Non invasive evaluation of portal hypertension using transient elastography. J Hepatol 2012; 56:696-703.
56) Augustin S, Millan L, Gonzalez A, Martell M, Gelabert A, Segarra A, et al. Detection of early portal hypertension with routine data and liver stiffness in patients with asymptomatic liver disease: a prospective study. J Hepatol 2014;60:561-569.
57) Robic MA, Procopet B, Metivier S, Peron JM, Selves J, Vinel JP, et al. Liver stiffness accurately predicts portal hypertension related complications in patients with chronic liver disease: a prospective study. J Hepatol 2011;55:1017-1024.
58) Colecchia A, Montrone L, Scaioli E, Bacchi-Reggiani ML, Colli A, Casazza G, et al. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. Gastroenterology 2012;143:646-654.

59) Colecchia A, Colli A, Casazza G, Mandolesi D, Schiumerini R, Reggiani LB, et al. Spleen stiffness measurement can predict clinical complications in compensated HCV-related cirrhosis: a prospective study. J Hepatol 2014;60:1158-1164.
60) Takuma Y, Nouso K, Morimoto Y, Tomokuni J, Sahara A, Toshikuni N, et al. Measurement of spleen stiffness by acoustic radiation force impulse imaging identifies cirrhotic patients with esophageal varices. Gastroenterology 2013;144:92-101.
61) Elkrief L, Rautou PE, Ronot M, Lambert S, Dioguardi BM, Francoz C, et al. Prospective comparison of spleen and liver stiffness by using shear-wave and transient elastography for detection of portal hypertension in cirrhosis. Radiology 2015; 275:589-598.
62) **Procopet B, Berzigotti A,** Abraldes JG, Turon F, Hernandez-Gea V, Garcia-Pagan JC, et al. Real-time shear-wave elastography: applicability, reliability and accuracy for clinically significant portal hypertension. J Hepatol 2015;62:1068-1075.
63) Singh S, Venkatesh SK, Loomba R, Wang Z, Sirlin C, Chen J, et al. Magnetic resonance elastography for staging liver fibrosis in non-alcoholic fatty liver disease: a diagnostic accuracy systematic review and individual participant data pooled analysis. Eur Radiol 2016;26:1431-1440.
64) Asrani SK, Talwalkar JA, Kamath PS, Shah VH, Saracino G, Jennings L, et al. Role of magnetic resonance elastography in compensated and decompensated liver disease. J Hepatol 2014; 60:934-939.
65) Ding NS, Nguyen T, Iser DM, Hong T, Flanagan E, Wong A, et al. Liver stiffness plus platelet count can be used to exclude high-risk oesophageal varices. Liver Int 2016;36:240-245.
66) Berzigotti A, Merkel C, Magalotti D, Tiani C, Gaiani S, Sacerdoti D, et al. New abdominal collaterals at ultrasound: a clue of progression of portal hypertension. Dig Liver Dis 2008;40:62-67.
67) Berzigotti A, Zappoli P, Magalotti D, Tiani C, Rossi V, Zoli M. Spleen enlargement on follow-up evaluation: a noninvasive predictor of complications of portal hypertension in cirrhosis. Clin Gastroenterol Hepatol 2008;6:1129-1134.
68) Di Marco V, Calvaruso V, Ferraro D, Bavetta MG, Cabibbo G, Conte E, et al. Effects of eradicating hepatitis C virus infection in patients with cirrhosis differ with stage of portal hypertension. Gastroenterology 2016;151:130-139.
69) **Abraldes JG**, **Tarantino I**, Turnes J, Garcia-Pagan JC, Rodes J, Bosch J. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. Hepatology 2003;37:902-908.
70) D'Amico G, Garcia-Pagan JC, Luca A, Bosch J. HVPG reduction and prevention of variceal bleeding in cirrhosis. A systematic review. Gastroenterology 2006;131:1611-1624.
71) Villanueva C, Aracil C, Colomo A, Hernandez-Gea V, Lopez-Balaguer JM, Alvarez-Urturi C, et al. Acute hemodynamic response to beta-blockers and prediction of long-term outcome in primary prophylaxis of variceal bleeding. Gastroenterology 2009;137:119-128.
72) La Mura V, Abraldes JG, Raffa S, Retto O, Berzigotti A, Garcia-Pagan JC, et al. Prognostic value of acute hemodynamic response to i.v. propranolol in patients with cirrhosis and portal hypertension. J Hepatol 2009;51:279-287.
73) Nagula S, Jain D, Groszmann RJ, Garcia-Tsao G. Histological-hemodynamic correlation in cirrhosis-a histological classification of the severity of cirrhosis. J Hepatol 2006;44:111-117.
74) Garcia-Tsao G, Friedman S, Iredale J, Pinzani M. Now there are many (stages) where before there was one: In search of a pathophysiological classification of cirrhosis. Hepatology 2010; 51:1445-1449.
75) Yoon YJ, Friedman SL, Lee YA. Antifibrotic therapies: where are we now? Semin Liver Dis 2016;36:87-98.
76) **Abraldes JG**, **Albillos A**, Banares R, Turnes J, Gonzalez R, Garcia-Pagan JC, et al. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized controlled trial. Gastroenterology 2009;136:1651-1658.
77) Mohanty A, Tate JP, Garcia-Tsao G. Statins are associated with a decreased risk of decompensation and death in veterans with hepatitis C-related compensated cirrhosis. Gastroenterology 2016;150:430-440.
78) Hernandez-Gea V, Aracil C, Colomo A, Garupera I, Poca M, Torras X, et al. Development of ascites in compensated cirrhosis with severe portal hypertension treated with beta-blockers. Am J Gastroenterol 2012;107:418-427.
79) Reiberger T, Ulbrich G, Ferlitsch A, Payer BA, Schwabl P, Pinter M, et al. Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. Gut 2013;62:1634-1641.
80) Turnes J, Garcia-Pagan JC, Abraldes JG, Hernandez-Guerra M, Dell'era A, Bosch J. Pharmacological reduction of portal pressure and long-term risk of first variceal bleeding in patients with cirrhosis. Am J Gastroenterol 2006;101:506-512.
81) The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices. A prospective multicenter study. N Engl J Med 1988;319:983-989.
82) Gluud LL, Krag A. Banding ligation versus beta-blockers for primary prevention in oesophageal varices in adults. Cochrane Database Syst Rev 2012;(8):CD004544.
83) Li L, Yu C, Li Y. Endoscopic band ligation versus pharmacological therapy for variceal bleeding in cirrhosis: a meta-analysis. Can J Gastroenterol 2011;25:147-155.
84) Tripathi D, Ferguson JW, Kochar N, Leithead JA, Therapondos G, McAvoy NC, et al. Randomized controlled trial of carvedilol versus variceal band ligation for the prevention of the first variceal bleed. Hepatology 2009;50:825-833.
85) Shah HA, Azam Z, Rauf J, Abid S, Hamid S, Jafri W, et al. Carvedilol vs. esophageal variceal band ligation in the primary prophylaxis of variceal hemorrhage: a multicentre randomized controlled trial. J Hepatol 2014;60:757-764.
86) Longacre AV, Imaeda A, Garcia-Tsao G, Fraenkel L. A pilot project examining the predicted preferences of patients and physicians in the primary prophylaxis of variceal hemorrhage. Hepatology 2008;47:169-176.
87) Yan K, Bridges JF, Augustin S, Laine L, Garcia-Tsao G, Fraenkel L. Factors impacting physicians' decisions to prevent variceal hemorrhage. BMC Gastroenterol 2015;15:55.
88) Sarin SK, Wadhawan M, Agarwal SR, Tyagi P, Sharma BC. Endoscopic variceal ligation plus propranolol versus endoscopic variceal ligation alone in primary prophylaxis of variceal bleeding. Am J Gastroenterol 2005;100:797-804.
89) D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. Hepatology 1995;22: 332-354.
90) Merkel C, Marin R, Angeli P, Zanella P, Felder M, Bernardinello E, et al. A placebo-controlled clinical trial of nadolol in the prophylaxis of growth of small esophageal varices in cirrhosis. Gastroenterology 2004;127:476-484.
91) Bhardwaj A, Kedarisetty CK, Vashishtha C, Bhadoria AS, Jindal A, Kumar G, et al. Carvedilol delays the progression of small oesophageal varices in patients with cirrhosis: a randomised placebo-controlled trial. Gut 2016 Jun 13. pii: gutjnl-

2016-311735. doi: 10.1136/gutjnl-2016-311735. [Epub ahead of print]
92) Sarin SK, Mishra SR, Sharma P, Sharma BC, Kumar A. Early primary prophylaxis with beta-blockers does not prevent the growth of small esophageal varices in cirrhosis: a randomized controlled trial. Hepatol Int 2013;7:248-256.
93) Cales P, Oberti F, Payen JL, Naveau S, Guyader D, Blanc P, et al. Lack of effect of propranolol in the prevention of large oesophageal varices in patients with cirrhosis: a randomized trial. French-Speaking Club for the Study of Portal Hypertension. Eur J Gastroenterol Hepatol 1999;11:741-745.
94) Augustin S, Muntaner L, Altamirano JT, Gonzalez A, Saperas E, Dot J, et al. Predicting early mortality after acute variceal hemorrhage based on classification and regression tree analysis. Clin Gastroenterol Hepatol 2009;7:1347-1354.
95) Villanueva C, Colomo A, Bosch A, Concepcion M, Hernandez-Gea V, Aracil C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013;368:11-21.
96) Bosch J, Thabut D, Bendtsen F, D'Amico G, Albillos A, Gonzalez AJ, et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. Gastroenterology 2004;127:1123-1130.
97) Bosch J, Thabut D, Albillos A, Carbonell N, Spicak J, Massard J, et al. Recombinant factor VIIa for variceal bleeding in patients with advanced cirrhosis: a randomized, controlled trial. Hepatology 2008;.47:1604-1614.
98) Bernard B, Grange JD, Khac EN, Amiot X, Opolon P, Poynard T. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. Hepatology 1999;29:1655-1661.
99) Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila F, Soares-Weiser K, Mendez-Sanchez N, Gluud C, et al. Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding—an updated Cochrane review. Aliment Pharmacol Ther 2011;34:509-518.
100) Pauwels A, Mostefa-Kara N, Debenes B, Degoutte E, Levy VG. Systemic antibiotic prophylaxis after gastrointestinal hemorrhage in cirrhotic patients with a high risk of infection. Hepatology 1996;24:802-806.
101) Fernandez J, Ruiz dA, Gomez C, Durandez R, Serradilla R, Guarner C, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. Gastroenterology 2006;131:1049-1056.
102) Wells M, Chande N, Adams P, Beaton M, Levstik M, Boyce E, et al. Meta-analysis: vasoactive medications for the management of acute variceal bleeds. Aliment Pharmacol Ther 2012; 35:1267-1278.
103) Seo YS, Park SY, Kim MY, Kim JH, Park JY, Yim HJ, et al. Lack of difference among terlipressin, somatostatin, and octreotide in the control of acute gastroesophageal variceal hemorrhage. Hepatology 2014;60:954-963.
104) Monescillo A, Martinez-Lagares F, Ruiz-del-Arbol L, Sierra A, Guevara C, Jimenez E, et al. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. Hepatology 2004;40:793-801.
105) Garcia-Pagán JC, Caca K, Bureau C, Laleman W, Appenrodt B, Luca A, et al.; Early TIPS (Transjugular Intrahepatic Portosystemic Shunt) Cooperative Study Group. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med 2010;362:2370-2379.
106) Garcia-Pagán JC, Di Pascoli M, Caca K, Laleman W, Bureau C, Appenrodt B, et al. Use of early-TIPS for high-risk variceal bleeding: results of a post-RCT surveillance study. J Hepatol 2013;58:45-50.
107) Rudler M, Cluzel P, Corvec TL, Benosman H, Rousseau G, Poynard T, et al. Early-TIPSS placement prevents rebleeding in high-risk patients with variceal bleeding, without improving survival. Aliment Pharmacol Ther 2014;40:1074-1080.
108) Escorsell A, Pavel O, Cardenas A, Morillas R, Llop E, Villanueva C, et al. Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: A multicenter randomized, controlled trial. Hepatology 2016; 63:1957-1967.
109) Puente A, Hernandez-Gea V, Graupera I, Roque M, Colomo A, Poca M, et al. Drugs plus ligation to prevent rebleeding in cirrhosis: an updated systematic review. Liver Int 2014;34:823-833.
110) Gluud LL, Langholz E, Krag A. Meta-analysis: isosorbide-mononitrate alone or with either beta-blockers or endoscopic therapy for the management of oesophageal varices. Aliment Pharmacol Ther 2010;32:859-871.
111) Stanley AJ, Dickson S, Hayes PC, Forrest EH, Mills PR, Tripathi D, et al. Multicentre randomised controlled study comparing carvedilol with variceal band ligation in the prevention of variceal rebleeding. J Hepatol 2014;61:1014-1019.
112) Lo GH, Chen WC, Wang HM, Yu HC. Randomized, controlled trial of carvedilol versus nadolol plus isosorbide mononitrate for the prevention of variceal rebleeding. J Gastroenterol Hepatol 2012;27:1681-1687.
113) **Abraldes JG, Villanueva C,** Aracil C, Turnes J, Hernandez-Guerra M, Genesca J, et al. Addition of simvastatin to standard therapy for the prevention of variceal rebleeding does not reduce rebleeding but increases survival in patients with cirrhosis. Gastroenterology 2016;150:1160-1170.
114) Boyer TD, Haskal ZJ. The role of transjugular intrahepatic portosystemic shunt (TIPS) in the management of portal hypertension: update 2009. Hepatology 2010;51:306.
115) Holster IL, Tjwa ET, Moelker A, Wils A, Hansen BE, Vermeijden JR, et al. Covered transjugular intrahepatic portosystemic shunt versus endoscopic therapy + beta-blocker for prevention of variceal rebleeding. Hepatology 2016;63:581-589.
116) Sauerbruch T, Mengel M, Dollinger M, Zipprich A, Rossle M, Panther E, et al. Prevention of rebleeding from esophageal varices in patients with cirrhosis receiving small-diameter stents versus hemodynamically controlled medical therapy. Gastroenterology 2015;149:660-668.
117) Sarin SK, Lahoti D, Saxena SP, Murthy NS, Makwana UK. Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients. Hepatology 1992;16:1343-1349.
118) Kim T, Shijo H, Kokawa H, Tokumitsu H, Kubara K, Ota K, et al. Risk factors for hemorrhage from gastric fundal varices. Hepatology 1997;25:307-312.
119) Mishra SR, Sharma BC, Kumar A, Sarin SK. Primary prophylaxis of gastric variceal bleeding comparing cyanoacrylate injection and beta-blockers: a randomized controlled trial. J Hepatol 2011;54:1161-1167.
120) Rios CE, Seron P, Gisbert JP, Bonfill Cosp X. Endoscopic injection of cyanoacrylate glue versus other endoscopic procedures for acute bleeding gastric varices in people with portal hypertension. Cochrane Database Syst Rev 2015;(5): CD010180.
121) El Amin H, Abdel BL, Sayed Z, Abdel ME, Eid K, Fouad Y, et al. A randomized trial of endoscopic variceal ligation versus cyanoacrylate injection for treatment of bleeding junctional varices. Trop Gastroenterol 2010;31:279-284.
122) Bhat YM, Weilert F, Fredrick RT, Kane SD, Shah JN, Hamerski CM, et al. EUS-guided treatment of gastric fundal

varices with combined injection of coils and cyanoacrylate glue: a large U.S. experience over 6 years (with video). Gastrointest Endosc 2016;83:1164-1172.
123) Caldwell S. Gastric varices: is there a role for endoscopic cyanoacrylates, or are we entering the BRTO era? Am J Gastroenterol 2012;107:1784-1790.
124) Kahloon A, Chalasani N, DeWitt J, Liangpunsakul S, Vinayek R, Vuppalanchi R, et al. Endoscopic therapy with 2-octyl-cyanoacrylate for the treatment of gastric varices. Dig Dis Sci 2014;59:2178-2183.
125) Bhat YM, Banerjee S, Barth BA, Chauhan SS, Gottlieb KT, Konda V, et al. Tissue adhesives: cyanoacrylate glue and fibrin sealant. Gastrointest Endosc 2013;78:209-215.
126) Chau TN, Patch D, Chan YW, Nagral A, Dick R, Burroughs AK. Salvage transjugular intrahepatic portosystemic shunts—gastric fundal compared with esophageal variceal bleeding. Gastroenterology 1998;114:981-987.
127) Mishra SR, Chander SB, Kumar A, Sarin SK. Endoscopic cyanoacrylate injection versus beta-blocker for secondary prophylaxis of gastric variceal bleed: a randomised controlled trial. Gut 2010;59:729-735.
128) Hung HH, Chang CJ, Hou MC, Liao WC, Chan CC, Huang HC, et al. Efficacy of non-selective beta-blockers as adjunct to endoscopic prophylactic treatment for gastric variceal bleeding: a randomized controlled trial. J Hepatol 2012;56:1025-1032.
129) Lo GH, Liang HL, Chen WC, Chen MH, Lai KH, Hsu PI, et al. A prospective, randomized controlled trial of transjugular intrahepatic portosystemic shunt versus cyanoacrylate injection in the prevention of gastric variceal rebleeding. Endoscopy 2007;39:679-685.
130) Fukuda T, Hirota S, Sugimura K. Long-term results of balloon-occluded retrograde transvenous obliteration for the treatment of gastric varices and hepatic encephalopathy. J Vasc Interv Radiol 2001;12:327-336.
131) Saad WE. Balloon-occluded retrograde transvenous obliteration of gastric varices: concept, basic techniques, and outcomes. Semin Intervent Radiol 2012;29:118-128.
132) Saad WE, Sze DY. Variations of balloon-occluded retrograde transvenous obliteration (BRTO): balloon-occluded antegrade transvenous obliteration (BATO) and alternative/adjunctive routes for BRTO. Semin Intervent Radiol 2011;28:314-324.
133) Gwon DI, Kim YH, Ko GY, Kim JW, Ko HK, Kim JH, et al. Vascular plug-assisted retrograde transvenous obliteration for the treatment of gastric varices and hepatic encephalopathy: a prospective multicenter study. J Vasc Interv Radiol 2015;26:1589-1595.
134) Lee EW, Saab S, Gomes AS, Busuttil R, McWilliams J, Durazo F, et al. Coil-assisted retrograde transvenous obliteration (CARTO) for the treatment of portal hypertensive variceal bleeding: preliminary results. Clin Transl Gastroenterol 2014;5:e61.
135) Norton ID, Andrews JC, Kamath PS. Management of ectopic varices. HEPATOLOGY 1998;28:1154-1158.
136) Henry Z, Uppal D, Saad W, Caldwell S. Gastric and ectopic varices. Clin Liver Dis 2014;18:371-388.
137) Serste T, Melot C, Francoz C, Durand F, Rautou PE, Valla D, et al. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. HEPATOLOGY 2010;52:1017-1022.
138) Serste T, Francoz C, Durand F, Rautou PE, Melot C, Valla D, et al. Beta-blockers cause paracentesis-induced circulatory dysfunction in patients with cirrhosis and refractory ascites: a cross-over study. J Hepatol 2011;55:794-799.
139) Mandorfer M, Bota S, Schwabl P, Bucsics T, Pfisterer N, Kruzik M, et al. Nonselective beta blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. Gastroenterology 2014;146:1680-1690.
140) Leithead JA, Rajoriya N, Tehami N, Hodson J, Gunson BK, Tripathi D, et al. Non-selective beta-blockers are associated with improved survival in patients with ascites listed for liver transplantation. Gut 2015;64:1111-1119.
141) Bossen L, Krag A, Vilstrup H, Watson H, Jepsen P. Non-selective beta-blockers do not affect mortality in cirrhosis patients with ascites: post hoc analysis of three RCTs with 1198 patients. HEPATOLOGY 2016;63:1968-1976.
142) Bang UC, Benfield T, Hyldstrup L, Jensen JB, Bendtsen F. Effect of propranolol on survival in patients with decompensated cirrhosis: a nationwide study based Danish patient registers. Liver Int 2016;36:1304-1312.
143) Mookerjee RP, Pavesi M, Thomsen KL, Mehta G, MacNaughtan J, Bendtsen F, et al.; CANONIC Study Investigators of the EASL-CLIF Consortium. Treatment with non-selective beta-blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure. J Hepatol 2016;64:574-582.
144) Madsen BS, Nielsen KF, Fialla AD, Krag A. Keep the sick from harm in spontaneous bacterial peritonitis: Dose of beta blockers matters. J Hepatol 2016;64:1455-1456.
145) de Souza AR, La Mura V, Reverter E, Seijo S, Berzigotti A, Ashkenazi E, et al. Patients whose first episode of bleeding occurs while taking a beta-blocker have high long-term risks of rebleeding and death. Clin Gastroenterol Hepatol 2012;10:670-676; quiz, e58.
146) Poynard T, Lebrec D, Hillon P, Sayegh R, Bernuau J, Naveau S, et al. Propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: a prospective study of factors associated with rebleeding. HEPATOLOGY 1987;7:447-451.
147) Singal AK, Jampana SC, Singal V, Kuo YF. Hepatocellular carcinoma predicts in-hospital mortality from acute variceal hemorrhage among patients with cirrhosis. J Clin Gastroenterol 2012;46:613-619.
148) Ripoll C, Genesca J, Araujo IK, Graupera I, Augustin S, Tejedor M, et al. Rebleeding prophylaxis improves outcomes in patients with hepatocellular carcinoma. A multicenter case-control study. HEPATOLOGY 2013;58:2079-2088.

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